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EXTRAPLEURAL THORACOPLASTY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

WILLIAM H. THEARLE[3]

The development of thoracoplasty has passed through three interesting periods. The names of Simon, Heineche, Estlander, and Schede are connected with the various operative methods advocated during the early period for the closure of old tuberculous empyema cavities, which they endeavored to accomplish by liberation of restricting adhesions, and thus secure reëxpansion of the lung. This is the converse of what we now aim to accomplish by thoracoplasty in pulmonary tuberculosis.

The second period is characterized by the thoracoplastic work of Quincke and Carl Spengler, who suggested the collapse of tuberculous cavities by resection of part of the upper ribs. Only a small number, however, of these operations, to which Spengler gave the name *extrapleural thoracoplasty*, was performed, as very little, if any, lasting improvement was attained by this rather limited or partial lung compression.

The adoption of artificial-pneumothorax therapy in pulmonary tuberculosis in the beginning of the present century ushered in the third developmental stage of thoracoplasty, the brilliant work of Brauer and Sauerbruch being conspicuous during this period. The extraordinarily beneficent effects of this therapy in properly selected cases of unilateral phthisis were soon demonstrated, and the experiences thus gained explained the poor results previously attained in partial plastic operations. Brauer, with his extensive pneumothorax experience and his keen surgical imagination, conceived the idea of collapsing the lung in cases in which pleural adhesions rendered pneumothorax impossible, by an extensive resection of the major portions of all the ribs on one side of the chest.

He suggested this surgical procedure to Friedrich, his surgical colleague at Marburg, and the latter performed this formidable operation on a

[1] Read before the Medical Society of the City and County of Denver, Colorado, January 15, 1924.

[2] Published by permission of the Surgeon-General, United States Army.

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Belgian in December, 1907, under general anesthesia. This is the Friedrich-Brauer thoracoplasty which is associated with considerable shock and chest deformity, a very high mortality, and alarming sequellae for some days (marked dyspnea and air hunger, with paradoxical breathing and pendulum air due to loss of bony support, mediastinal flutter, and cardiac embarrassment from unsupported heart, sputum retention, aspiration dangers, pulmonary edema). Its use for collapse therapy in tuberculosis has therefore been abandoned, although in some exceptional cases of large pyopneumothoraces and tuberculous empyemas it may advantageously be employed as a several-stage operation. The pyramidal resection of Wilms, anteriorly and posteriorly performed in stages, has not gained in favor in phthisical therapy, as the collapse obtained was incomplete and its results inferior to the technical surgical collapse developed and standardized by Sauerbruch, which is the operation at present understood under the term *extrapleural thoracoplasty*. It consists briefly in the subperiosteal resection of various lengths of the first or second to the tenth or eleventh ribs, posteriorly; the operation is always begun over the lower lobe, and is preferably performed in one stage, but frequently two are necessary.

The aim of the operation is to compress the lung by approximation of the resected ribs and thus place the lung at physiological rest, which is the prime desideratum in tuberculosis therapy. The fixation points of the ribs are posteriorly at the costovertebral articulations, while the sternal ends of the ribs are somewhat flexible. The importance of resecting the ribs close to the vertebrae in order to secure a good collapse, as well as the rationale of the paravertebral operation, is thus quite obvious. Section of the ribs in this manner results in a diminution of both the transverse and sagittal diameters, as well as a downward shift of the chest wall of one or two interspaces, with section of the upper two ribs and especially the first.

The flexibility of the ribs in the uppermost portion of the thorax is materially less than in the lower part, and the degree of lung compression obtained by resection is correspondingly less. The frequency of cavitation in pulmonary tuberculosis in the upper lobes or apices compels us to resort to partial collapse in such cases, which is best accomplished by the apicolysis operation devised by Tuffier. This procedure consists in an anterior resection of the second rib; the pleura with the underlying adherent lung is then stripped by hand from the thoracic wall, being careful to keep outside the parietal pleura. The collapse thus secured is

maintained by filling the space thus created with an autogenous fat transplant. Baer tampons this area with paraffin but this has not proved satisfactory, while Archibald maintains compression by pedicle flaps of muscle.

Indications for surgical collapse are largely the same as for pneumothorax, a simple but trenchant rule being: *thoracoplasty is indicated for those patients who should have an artificial pneumothorax, but in whom a pneumothorax is impossible on account of pleural adhesions.* Essentially the indications are:

(1) Unilateral pulmonary involvement, or, if a lesion is present in the other lung, which is usually the case in chronic phthisis, that it be slight or arrested.

(2) That artificial pneumothorax shall have been tried and found impracticable.

The assistance and counsel of a specialist in tuberculosis is so indispensable in the selection of proper cases as to practically constitute an indication in this therapy.

The class of patients especially suitable for operation belong to the group of chronic fibrous phthisis with cavitation, which is commonly multiple. Their lungs show shrinkage, and their chests usually retraction due to the fibrosis, associated with their pulmonary destruction, which causes the diaphragm to be pulled up, and their mediastinal viscera to be displaced and often fixed. Nature, however, is unable to effect a cure, as such cavities remain open, because of the rigidity of the ribs and the fibrous adhesions of the lung and pleura to the chest wall. The majority of this class pursue a slowly downward course, although this may be interrupted by brief stationary periods or times of slight improvement. Their prognosis is bad, in fact, more often hopeless, and death eventually claims them through amyloid visceral complications from years of pulmonary sepsis, unless their demise is brought about earlier by pulmonary hemorrhage or some intercurrent disease.

Surgical collapse is also indicated in a fair percentage of chronic cases with mainly unilateral involvement for repeated hemorrhages, when pneumothorax is impossible, as well as in a certain number of pyopneumothoraces.

Contraindications are: (1) no attempt has been made at artificial pneumothorax, (2) too extensive involvement of the better lung, (3)

miliary tuberculosis, (4) tuberculous peritonitis, (5) amyloid visceral changes, (6) nephritis, or any serious disease elsewhere in the body.

A complete preoperative expectoration, or rather emptying of cavities to minimize the dangers of sputum aspiration, is perhaps the most important feature in the *preparation of the patient.* This is accomplished posturally by education of the patient. The present condition of the kidneys is determined (blood chemistry, functional tests, urinalysis, 24-hour fluid intake, and urine elimination and, in questionable cases, other special tests). A donor is obtained for blood transfusion, if needed, and all cases are digitalized. One hour before operation the patient is given morphine, gr. $\frac{1}{4}$, with scopolamine, gr. 1/150, and the morphine is repeated at the time of operation.

Operation is performed under local and paravertebral novocaine anesthesia; and Sauerbruch's procedure is followed, except that longer sections of ribs are removed beneath the scapula, as advised by Brauer in his paravertebral subscapular resection. The wound is closed in layers with rubber tissue drains extending through muscle planes, and the operated half of chest is tightly strapped with adhesive plaster.

We believe that these operations should be performed under local anesthesia alone, and that the addition of a general anesthetic does increase the risk through aspiration. It is not because of the irritation of the lungs by nitrous oxide gas, which is negligible, but the lack of a cough reflex incident to such anesthesia prevents the patient from coughing out material necessarily expressed from cavities, since these are collapsed during operation.

Resection of the eleventh rib is not always considered necessary, because the cavitation is usually located higher in the lung, and removal of this rib robs the diaphragm of some of its support, which increases the occurrence of diaphragmatic flutter. We do advise, though, resection of the first rib, which is usually somewhat difficult, as the frequency of apical cavities makes it desirable to secure a good collapse in this location, and it will frequently be found necessary to supplement thoracoplasty with apicolysis in order to obtain an efficient collapse at the apex.

A one-stage operation is preferable, and it is quite important that it be performed as expeditiously as possible, consistent with good surgical technique. The patient's condition has not warranted resection of the first rib in many of our thoracoplasties, especially in a one-stage operation.

During operation the pulse rate often rises to 120 or 140, and the respirations to 40; shock and hemorrhage of variable degrees (dependent on the physical condition of the patient) are present.

POSTOPERATIVE PERIOD AND COMPLICATIONS

The first few days after operation is usually the critical stage in these cases, and the fortunate outcome depends largely on the strength of the patient and the calm judgment of the surgeon, with close attention to details. A special nurse is very important. Treatment is usually symptomatic; morphine for pain and cough; saline proctoclysis; intravenous saline solution and blood transfusion, if indicated. Increased respiratory and cardiac rates, as well as dyspnea are present for some days. The latter at times may be quite labored and alarming, with cyanosis due to cardiac embarrassment from the changed relations of the thoracic viscera by operation. Fever, though usually of a moderate degree, is present for several days.

Sputum retention is combated by urging the patient to use energetic efforts at coughing during the first days after operation; the sputum rapidly becomes very tenacious, which, together with the loss of bony rigidity and corresponding weakness of thoracic muscles from operation and immobility of one-half of the chest, makes its expulsion difficult. The sputum is very soon markedly diminished in quantity, commensurate with the degree of collapse of the cavities.

The subsequent course of favorable cases after the first few days, barring complications, is usually progressive. The degree of chest deformity and scoliosis is dependent on the extensiveness of ribs removed, and is combated to some extent by early exercise with proper posture.

Complications are aspiration pneumonia, activation or aggravation of the disease in the better lung, cardiac failure, pulmonary hemorrhage, wound sepsis, nephritis, and amyloid visceral disease.

Results: This paper is based on an experience with 13 patients on whom an extrapleural thoracoplasty has been performed, mostly during the past year. All were adult males (except one) with ages varying from twenty-two to forty-five years. The chief involvement was on the left side in eight, and on the right in five cases. The patients were considered, at the time of operation, to be in good condition in three cases, in fair condition in four, and in poor condition in six.

The results, briefly, are as follows: Two, or 16 per cent, died from operation (one from pulmonary hemorrhage with asphyxiation, and the other from paralytic ileus). Two patients are unimproved, due to amyloid visceral changes and intestinal tuberculosis, which appeared soon after operation. They were both in poor condition and it was

questionable at the time of operation as to whether amyloid disease was present and really did not meet the operative indications. Six are markedly improved, but two of these were pyopneumothoraces and require further surgical collapse to obliterate small remaining cavities, which it is hoped will eventually result in their classification as cures. One case was slightly improved and two cases are classed as practical cures. Sauerbruch defines practical cures to imply disappearance of bacilli, almost complete disappearance of cough and sputum, a general feeling of well-being, and ability to do a certain amount of light work.

Statistics on the continent of Europe show healing in 30 per cent, with marked improvement in 30 per cent, and a mortality of 15 to 20 per cent. Sauerbruch, in his large series of 381 thoracoplasties, reports 35 per cent of cures, 40 per cent of marked improvement, and 14 per cent mortality, 2 per cent of which were operative. Archibald, in a series of 31 cases, reports 25 per cent cures, 17 per cent markedly improved, and 9.7 per cent operative mortality, with an 8.5 per cent late mortality due to progress of disease.

Brief histories of two cases, with presentation of five patients, and roentgenograms, will illustrate the salient features in this small operative series:

Case 1: F. C. Adult male, age 34, Italian, drafted into service in spring of 1918. He had always enjoyed good health, and personal history was negative except for an uncomplicated attack of influenza in 1914. He was sent to hospital in France in April, 1919, for bad cold, and examination showed pulmonary tuberculosis.

He was evacuated to the States and admitted to Fitzsimons General Hospital, as a litter case, in November, 1919, with diagnosis of tuberculosis, pulmonary, chronic, inactive, right lower lobe, but active in all other lobes of both lungs; examination otherwise negative.

There was perhaps a little improvement in this patient's condition for several months after admission, but he was more or less stationary, with occasional slight febrile periods of short duration until January, 1923. At this time he began to have pulmonary hemorrhages which continued at rather frequent intervals in amounts varying from 15 to 360 cc. and, as pneumothorax was impossible on account of pleural adhesions, a left thoracoplasty was advised last September. Diagnosis at that time was tuberculosis, pulmonary, chronic, all lobes both lungs, lesions in right lung being scattered and of fibrous type, while those in left lobes were active and of caseofibrous type with extensive cavitation of nearly whole upper lobe. Pulse 100 to 110 and blood pressure 98–70.

A one-stage operation was performed September 21 under novocaine anesthesia; 4 inches of 10th and 5 to 6 inches of 2nd to 9th left ribs were resected posteriorly. Pulse rose to 140 and blood pressure fell to 80–60 during operation; 800 cc. saline were given intravenously and usual treatment for shock, to which patient responded well. Blood pressure rose to 90 when he returned to ward. His pulse remained rapid, around 150, and the oozing from wound was a little more than usual; so he was given 500 cc. blood transfusion that night, without any reaction and with some improvement. Next day he was better, pulse 130 and blood pressure 96–75. He took liquids in small quantities. Dyspnea was slight, also cough and expectoration.

On September 23, condition was much improved but pulse continued around 130 in spite of digitalization; that night he had considerable abdominal distention and began to vomit. Everything was stopped by mouth; duodenal lavage and enemata with pituitrin gave some relief, but the next morning (September 24) his distention and vomiting became more marked. He was given a second blood transfusion and enterostomy was considered for ileus, but he rapidly grew worse and died shortly after noon. Postmortem showed marked intestinal distention and paralytic ileus as cause of death.

Case 2: I. G. Adult female, age 27, developed tuberculosis in France the winter of 1918, which was first diagnosed April, 1919, when she was evacuated to the States. She was admitted to this hospital October, 1920, with tuberculosis, pulmonary, chronic, active, both upper and lower lobes, with small cavitation in left upper lobe. She was discharged November, 1921, slightly improved with slight cough and expectoration, and some dyspnea with fatigue on exertion. Sputum repeatedly positive. She went to her home in Massachusetts, when her condition became worse and she returned to this section of the country where she has been under treatment in various hospitals without improvement. She was admitted to this hospital last September. *Preoperative diagnosis:* Tuberculosis, pulmonary, chronic, active, both lobes left, and right upper. Inactive, right lower lobe, with multiple cavitation, left lung. Considerable troublesome cough; $\frac{3}{4}$ cup sputum raised per day.

Patient was prepared for thoracoplasty but, in making the paravertebral injection in ninth interspace, she complained of sharp pain, her pulse became very rapid, and breathing shallow and labored, with cyanosis and marked dyspnea. She was given oxygen inhalations and stimulants, and in an hour was all right although her pulse was still a little rapid and she felt prostrated. Whether this startling reaction was due to air embolism or novocaine in the blood-stream we are not prepared to say.

On September 18 a left extrapleural thoracoplasty was done under novocaine anesthesia, the following ribs being resected posteriorly: 4 inches of

10th and 6 inches of 9th to 2nd. Pulse increased to 140 and blood pressure fell to 82–60. (Blood pressure 102–80 before operation.) She was given 1000 cc. saline intravenously, and treatment for shock, to which she reacted well. However, she was seriously ill for a week, with pulse of 120 to 130, temperature of 100° to 101°, considerable dyspnea with cyanosis, moderate renal suppression and signs of consolidation at base of right lung.

Her improvement after the first week has been progressive. She now has little cough, chiefly in morning, her sputum is slight and free from tubercle bacilli; she is now ambulatory. Her left lung is well collapsed, and the result attained in this case is truly gratifying.

CONCLUSIONS

1. Extrapleural thoracoplasty is an essential advance in the treatment of pulmonary tuberculosis.

2. Surgical collapse should be promptly resorted to in all cases of pulmonary tuberculosis that fulfill the indications for artificial pneumothorax, when the latter therapy is impossible because of pleural adhesions.

3. Thoracoplasty should be performed at a much earlier period in pulmonary tuberculosis to reduce the admittedly high mortality which is inevitable with late operation in an advanced stage of this disease.

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THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS BY THORACOPLASTIC COLLAPSE

ADRIAN V. S. LAMBERT AND JAMES ALEXANDER MILLER

It is now widely recognized that a considerable percentage of selected cases of pulmonary tuberculosis may be successfully treated by surgical operation. These cases are of a class almost certainly doomed to either death or hopeless invalidism under the more usual methods of treatment. An interesting record of the development of this field of surgery is contained in the medical literature and it is not our purpose to recapitulate this history, but simply to record the results of our experience based upon 20 cases treated during the past two and a half years by the Sauerbruch operation.

GENERAL CONSIDERATIONS

The guiding principles in the consideration of this operative treatment are very similar to those applicable to that by artificial pneumothorax. In fact, almost invariably artificial pneumothorax should first be attempted before considering surgery.

In general, therefore, suitable cases should have predominantly unilateral lesions. A small apical lesion in the opposite lung, provided it is not active, does not constitute a contraindication, but lesions of the central and lower portion of the opposite lung usually preclude operation.

Prolonged observation with special reference to the X-ray findings, both before and after operation, is important. It must be constantly borne in mind that these cases, even though they may be rendered symptom-free by the operation, still have extensive pulmonary tuberculosis which requires prolonged after-care by accepted methods, and especially by rest.

The proper selection of suitable cases is the most important single element in success, and in this selection the appraisal of the general condition of the patient and of the condition of the opposite lung is the vital factor.

There are certain risks in the operative procedure which do not obtain in artificial pneumothorax. There is, in the first place, a certain operative mortality; at present, from 5 to 15 per cent. There is also an increased liability to a stirring up of the tuberculous lesions in the opposite lung, and, finally, after operation the lung collapse is permanent and the lung cannot be reëxpanded even though one might much desire to do so.

From the above considerations it is evident that success can only be assured by the close and consistent joint study of these cases, both before and after operation, on the part of the surgeon and an internist familiar with tuberculosis and with artificial-pneumothorax treatment.

SELECTION OF CASES

In addition to the above general principles the selection of suitable cases depends upon the consideration of certain specific conditions which have divided the cases into five fairly distinct types:

1. Long-standing chronic cases with a considerable degree of fibrosis, with or without cavity formation, constitute the largest group in which this operation is indicated, but only after artificial pneumothorax has been unsuccessfully tried and when the case continues to present progressive or intermittent evidence of activity of disease. In this group the patients who are in fair general condition and fair degree of nutrition are the better risks and preliminary rest treatment to obtain this result is desirable. There were 10 of these cases in our series.

2. Cases in which pneumothorax has been employed with only partial success due to localized adhesions. Our series contains 6 of these cases.

3. Acute unilateral lesions may be operated upon only after previous treatment by artificial pneumothorax with more or less favorable response. We operated upon two such cases.

4. Cases more or less successfully treated by artificial pneumothorax in which a chronic condition of tuberculous pyopneumothorax has developed. Thoracoplasty immediately following aspiration is the procedure indicated in these cases. Two such cases are in our series.

5. Cases in which artificial pneumothorax has been completely successful, in which the necessary periodic refills cannot be continued because of personal, economic or environmental conditions. We had one such case which was also included under the third type.

RESULTS

1. In the literature:

The accompanying table indicates the important points in the results reported by several observers to which our own are added for comparison.

	NUMBER OF CASES	OPERATIVE MORTALITY	LATE MORTALITY	TOTAL MORTALITY	CURED OR GREATLY IMPROVED
		per cent	*per cent*	*per cent*	*per cent*
Sauerbruch (1)	381	12			35
Gravesen (2)	105			9	41
Stöcklin[1] (3)	100			24	37
Bull (4)	92	10	25	35	45
Archibald[2] (5)	15	14	8.5	22.5	42
Lambert and Miller	20	15	15	30	55

We have not attempted to review all of the literature but have selected series which appear to be representative of the general experience of others.

Some reports are upon series of very small numbers of cases; others, such as Brauer's (6) very important contributions, do not present the results obtained in comparable form.

2. In the present series:

In addition to the outline report of the results which we have obtained in our 20 cases we desire to present them in the following form:

	NUMBER OF CASES	PER CENT
Operative deaths	3	15
Late deaths	3	15
Not improved	1	5
Improved	2	10
Apparently arrested	6	30
Arrested	5	25
Total	20	100

We consider a case as arrested and successful which has no tubercle bacilli in the sputum, no cough, no fever, has gained in weight and is able to return to active life. There are in this series 5 such cases or 25 per cent.

[1] Reports upon cases operated upon by Schreiber.

[2] Reports that series is now 31 cases with similar results.

A case is apparently arrested and tentatively successful which has no tubercle bacilli, no fever, occasional or no cough, has gained weight and is still taking a modified rest cure but is not considered able as yet to resume active life. There are 6 cases of this type, or 30 per cent.

A case is partially successful in which tubercle bacilli are present, but which has no fever, a slight morning and evening cough with small amounts of sputum, has gained weight, but is still under strict cure for tuberculosis. Two cases or 10 per cent fall into this group.

A case is a failure which has tubercle bacilli present in the sputum that is constant with cough, has occasional fever, and in which the weight is slightly improved. Under strict rest cure for tuberculosis. There is only one case of this type or 5 per cent.

The fatal cases we have divided into two groups, those which died as the immediate result of operation, of which there were 3 or 15 per cent, and those which succumbed to the disease within a year from extension of the pulmonary process to the contralateral lung. There are 3 cases of this character, or 15 per cent.

ANALYSIS OF FATAL CASES

We submit a rather detailed analysis of our 6 fatal cases, for the reason that the study of such unfortunate results affords the most likely basis for future progress in the selection of cases, in the technique of operation and in the estimation of the risks involved.

Case 1: H. S. A chronic ulcerative phthisis with extensive cavity formation, running an afebrile course with profuse expectoration and fairly well nourished. This operation was performed in one stage; the ten upper ribs, including the first, were removed under gas and oxygen anesthesia. She stood the operation well but succumbed within 48 hours. The amount of secretion suddenly poured out into her bronchi was great, and she was unable to cough it up, and her sound lung filled up, and she died with extreme respiratory distress and failure of cardiac action. This case but emphasizes the fact that a one-stage operation in the presence of large cavities is dangerous and should never be attempted. At present we do a multiple-stage operation from above downward. The upper portions of the chest are aerated mainly by the rise and fall of the ribs, while the lower portions, which are the more extensive, are mainly aerated by the excursions of the diaphragm, the expansions of the ribs increasing the size of the abdominal cavity to accommodate the descent of the diaphragm. By removing the upper ribs at the first stage we leave intact the power of the patient to cough, and so in-

terfere less with their expulsive efforts in the removal of expectoration from any collapsed cavities. We usually remove portions of the upper five ribs in the first stage, leaving the lower five for the second stage.

Case 2: F. H. A man with rather a melancholic type of mind who had been gassed during the war contracted tuberculosis and chafed a good deal over his inability to return to work. Following the operation, which went well, he developed a psychosis with ideas of persecution and a fixed delusion that everyone, including his family, were trying to poison him. He refused all forms of nourishment, including water, and literally wore himself out in ten days. The fatal result here we do not feel could have been anticipated, nor due to any fault in selection or technique, but due to conditions beyond our control.

Case 3: M. H. A young girl in which a one-stage operation was performed, in which pneumothorax was only partially successful on account of adhesions preventing a collapse of the cavity. She apparently did well during the first 12 hours following operation, but then began to have rapid breathing with slight acceleration of the pulse and slight cyanosis. The signs over the lower lobe of the contralateral lung were slightly impaired resonance, diminished or absence of breath sounds and a few fine râles. The temperature was slightly elevated, 100° to 101°. These signs gradually increased in extent, involving the lung from below upward. The cyanosis and dyspnea increased, and a few hours before death the pulse rate markedly increased, the temperature rose and she died with pronounced cyanosis. At autopsy there was found a massive collapse of the lung which, on section, did not show the changes of pneumonia but simply a series of collapsed vesicles. This is a very unusual accident, the cause of which as yet is not well understood. A number of cases have been reported following other operations but, so far as we know, this is the first case following thoracoplasty. Massive collapse is not usually fatal, as it occurs on one side only as a rule, but in this case, following operative collapse of the opposite lung, it was necessarily so. It is quite possible this accident would not have occurred if operation had been done in two stages.

Case 4: C. A. A young girl with acute pneumonic phthisis in whom artificial pneumothorax was attempted but unsuccessfully on account of adhesions. She did well following operation for about six weeks and developed an extension in the opposite lung and succumbed in four months.

It is quite possible that the outcome could not have been prevented but we now believe that acute cases should have been approached with greater caution than chronic, and that when artificial pneumothorax is not possible the operation should be performed in two, or possibly more, stages.

Case 5: P. S. A negro who had a low fever and was thought a favorable case for pneumothorax, but in whom the presence of adhesions rendered this impossible. He was operated upon in one stage and survived the operation, but died from an extension to the opposite side at the end of two months. This is another case in which a two-stage operation might probably have prevented the unfortunate outcome.

Case 6: J. D. A young man of deficient mentality and in a state of poor general nutrition, but seemingly favorable case although he had an extensive lesion. Following operation in one stage, he developed an extension in the opposite lung and died at the end of three months. It is possible that we erred in not taking time to build up his general condition before operation.

DISCUSSION OF FATAL CASES

In reviewing these operative deaths, it would now appear to us that in one case the fatal result could not have been foreseen.

In three cases it probably could have been avoided by a two-stage instead of a one-stage operation.

In one case it was probably a poor selection until the patient had been brought into a state of better general condition.

In one case death, resulting from the unusual accident of massive collapse of the opposite lung, might conceivably have been prevented by a two instead of one-stage operation.

We believe, therefore, that from our experience it may be possible for us to report a considerably lower percentage of mortality in the future.

CONCLUSIONS

1. It has been definitely demonstrated that thoracoplastic collapse of the lung is of very real value in the treatment of certain types of tuberculosis.

2. It is very closely associated and bound up with the problem of treatment by artificial pneumothorax.

3. At the present time approximately 50 per cent of carefully selected cases may be returned to a satisfactory degree of health.

4. The present mortality of approximately 25 per cent may probably be reduced in the future by better operative technique and more skilful selection of cases.

5. We now believe that only in the rarest exceptions should operation be performed in less than two stages.

6. The proper selection of cases is the most important single problem to be considered.

7. Cases so operated on still have their tuberculosis and must undergo prolonged after-treatment along approved methods of treatment of that disease, especially rest.

8. The success in treatment of these cases can only be obtained by the closest coöperation between physician and surgeon.

9. The judicious use of this operation will not only restore many hopeless invalids to economic independence but is a public health measure of importance, by rendering sputum-free a class of cases which are often a real menace to their associates.

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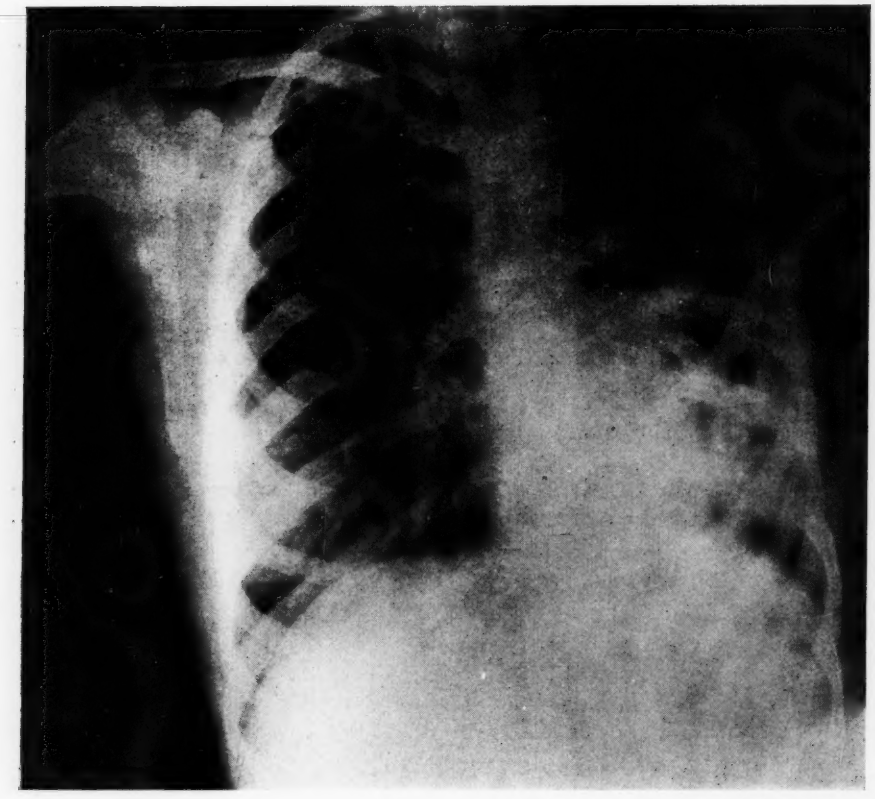

FIG. 1. RADIOGRAPH OF ONE OF THE PATIENTS BEFORE OPERATION

This patient belonged to the first of the five types described, that is, chronic unilateral disease, in which artificial pneumothorax was unsuccessfully tried.

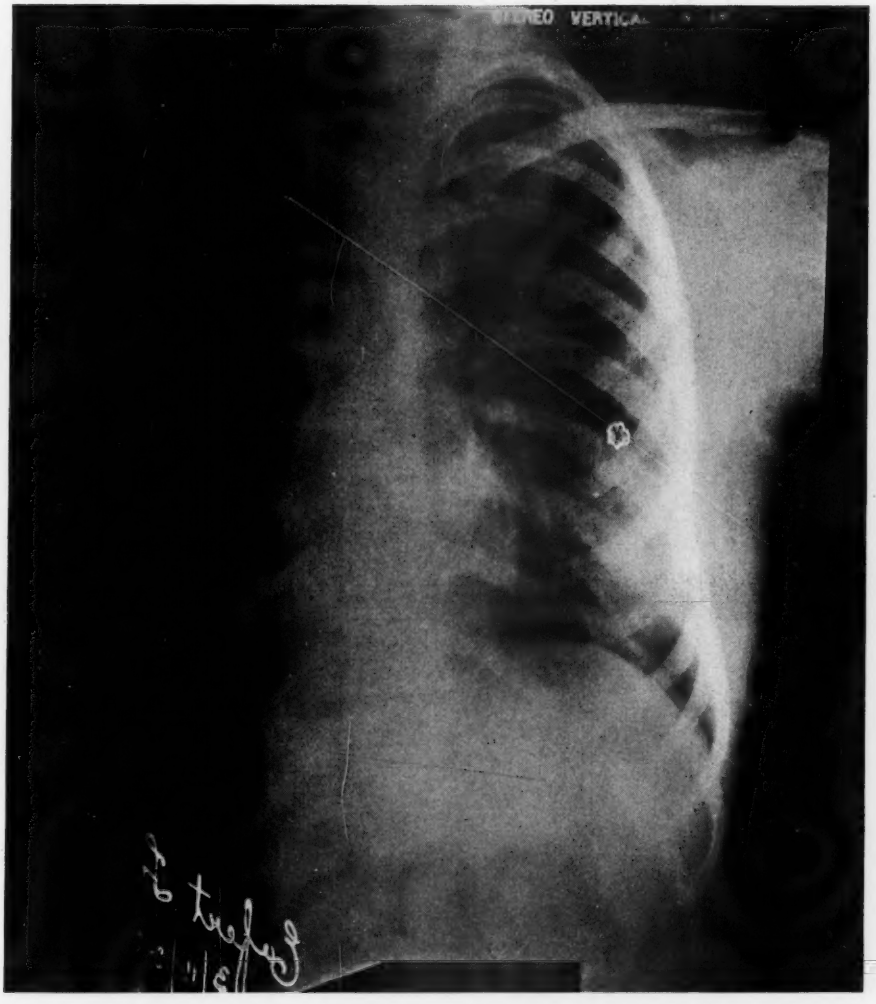

FIG. 2. RADIOGRAPH OF THE SAME PATIENT THREE MONTHS AFTER OPERATION

Shows the marked collapse of the lung and the regeneration of the ribs, longitudinally, along the periosteum which was left remaining, thus forming a firm bony cage for the chest in its new position.

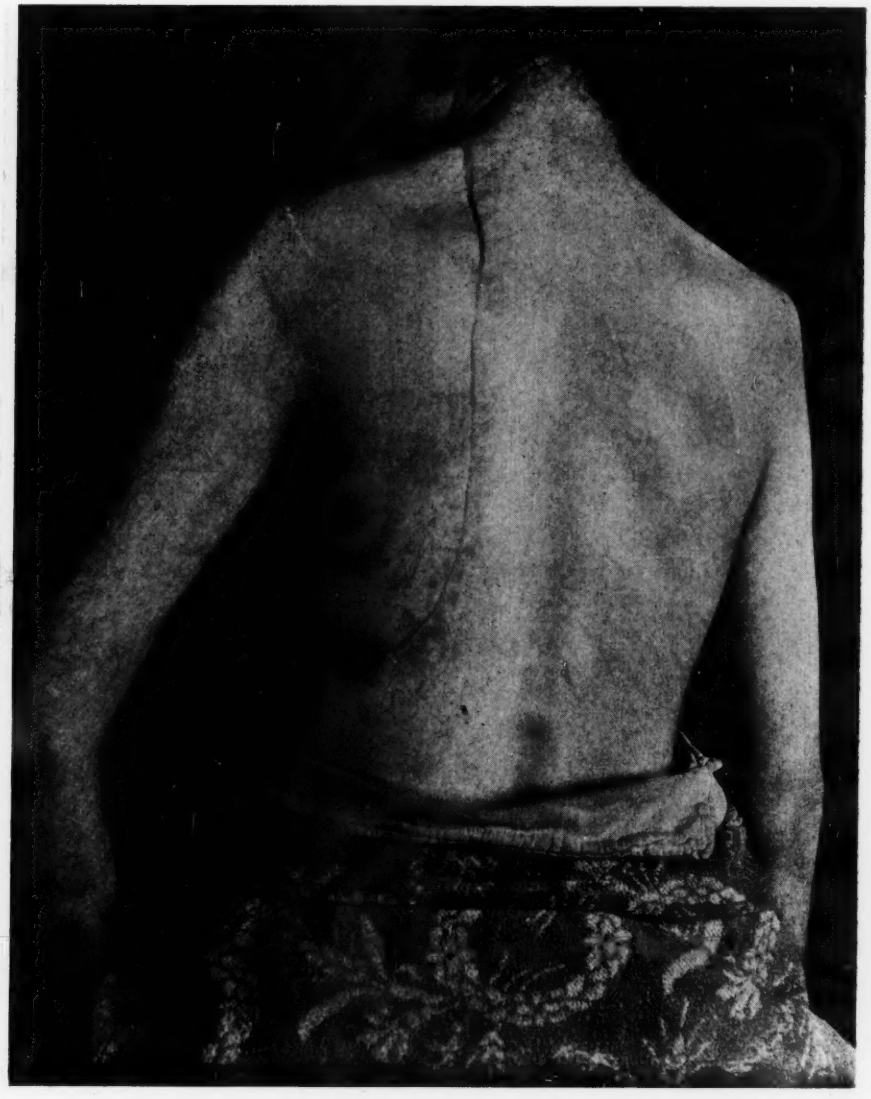

FIG. 3. SAME PATIENT SHOWING THE LINE OF INCISION

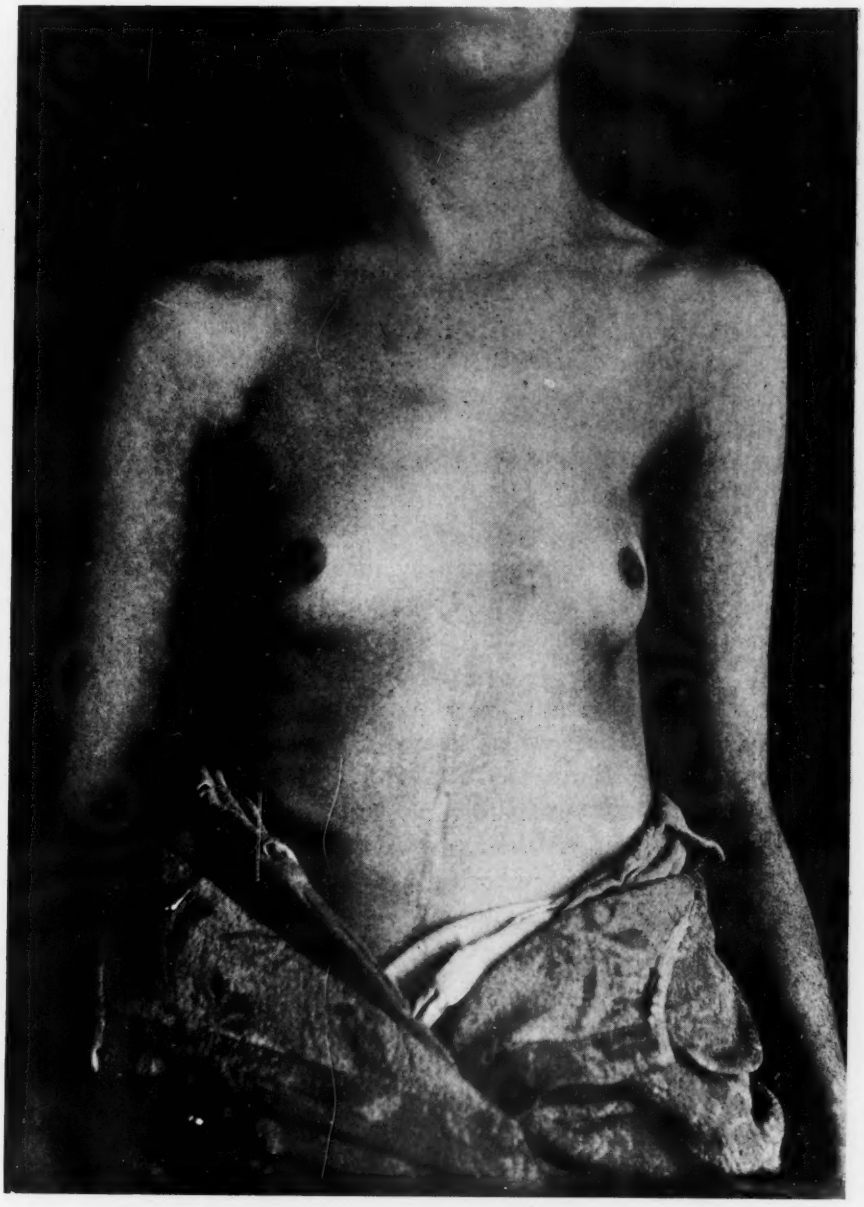

FIG. 4. ANTERIOR VIEW OF THE SAME PATIENT, SHOWING THE VERY MODERATE AMOUNT OF DEFORMITY AS COMPARED WITH COLLAPSE SHOWN IN THE RADIOGRAPH

This patient has been perfectly well and working regularly for the past two years

THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS[1]

EVERETT E. WATSON[2]

Ten years ago we began, at Mount Regis, to use artificial pneumothorax in the treatment of a selected number of more or less unilateral advanced cases who had failed to respond to the usual regimen of rest, etc., and who in our opinion presented little if any hope of improvement without collapse. Out of 117 cases, 79 (67.5 per cent) were completely or partially collapsed, and in 38 (32.5 per cent) no free pleural space could be found. Of these 38, only one is now arrested, 29 are dead, the remaining 9, with one exception, being bedridden. This plainly shows the type of cases chosen. While we have experienced many discouragements such as activation of the uncompressed lung, tuberculous empyemas, and "sticking," the fact, that of the 79 completely or partially collapsed cases we have been able to rehabilitate 20, who, for the time at least, are living comfortable and useful lives, sustains our enthusiasm. Our greatest disappointments have been due to our inability to compress, because of adhesions, cases which we considered ideal for the treatment, and in which in the past we have stood impotently by, watching while the disease progressed to a fatal termination.

We read with interest the reports of the work of Sauerbruch at the Marburg Clinic, who was removing the entire bony thorax on the affected side with an immediate mortality of almost 30 per cent. We must admit a lack of courage to advise such a formidable and mutilating operation. In 1916 Drs. Gale and Whitman removed for us all of the ribs, except the first, in a case which we briefly report.

Case 1: Mrs. G. C. M. Housewife, age 50, admitted October 9, 1915. Advanced left-sided involvement, complicated by tuberculous empyema. Marked emaciation (weight 64 pounds), temperature 102° to 103° daily, severe cough and profuse purulent expectoration. No improvement, and in December rib resection was done at the Sanatorium, as patient was too

[1] Read before the clinical section at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 7, 1924.

[2] Mount Regis Sanatorium, Salem, Virginia.

ill to move to the hospital. Following this there was some amelioration of symptoms; but the drainage continued, and during the following year the second to eleventh ribs, inclusive, were removed in their entirety, under local anesthesia, in several stages. There was gradual improvement and for the past seven years patient has done own housework and enjoyed good health, though at times there is still a very slight drainage.

Though the results were eminently satisfactory, this case impressed us as having had too painful and mutilating an operation to urge upon a patient, offering, as it did, no positive assurance of permanent benefit and not until 1920, four years later, did we undertake another.

Case 2: Mrs. M. E. C. Housewife, age 24, first seen by us in February, 1920. Tuberculosis had been diagnosed in March, 1914. Right lung had been collapsed and allowed to reëxpand. Following another breakdown in September, 1919, she again took sanatorium treatment, but the lung at this time could not be deflated and her physician had advised thoracoplasty. At this time patient was running temperature reaching 100° to 101° daily, and had severe cough and profuse sputum, which had an offensive odor not unlike that of a pulmonary abscess. X-ray examination in April, 1920, revealed a dense tuberculous infiltration of all of the right lung, most marked at base, with two cavities in 5th and 6th interspaces in posterior scapular line; also fibrosis in the left, back of 1st and 2nd interspaces, using anterior markings. This correlated fairly accurately with the physical findings. Under local anesthesia the 10th, 9th and 8th ribs were removed *in toto*, and several weeks later the 7th, 6th, 5th and 4th ribs. Compression bandages were applied and a fair degree of collapse, where most needed, was attained. There was some temporary improvement, but the contralateral lung went bad and she died two years later.

This case emphasized the importance of careful selection of patients for thoracoplastic collapse.

We next had two cases of intrapleural pneumolysis. In the first (case 3) a broad band of adhesions, which held open a large cavity, was severed by the open method. A perfect collapse was attained, but there was a stormy convalescence. For three and a half years the patient has been comparatively well but symptoms reappear when the lung reëxpands to any extent.

The other (case 4) was collapsed because of a large hilum abscess. This patient, a physician 54 years old, obtained a good collapse, but a short while later developed ulcerative colitis and died. Autopsy confirmed both diagnoses.

When a lung is worth saving and a band of adhesions is preventing effective collapse, this is the operation of choice. It, however, possesses evident dangers not met with in extrapleural collapse. Effusions occurred promptly, and two days after the operation in each case, serous fluid was withdrawn and replaced with air. When there has been great destruction of tissue, the posterior operation, as now advocated by Archibald, Lilienthal and others, would be simpler and probably, everything considered, more efficacious.

Case 5: M. A. R. Student, age 18. This patient entered Mount Regis in April, 1918, following profuse pulmonary hemorrhages. Though there was advanced involvement of the entire right lung, with early lesion at left apex, and Gaffky VI sputum, he improved after six months' bed-rest and was discharged after nine months, with no symptoms. Three months later was readmitted with advanced symptoms. Right lung was collapsed and six months later he was discharged. He went to work and did well until April, 1920, when, 12 hours after a deflation, he had a chill with an elevation of temperature to 104°. A purulent effusion rapidly formed. The high temperature continued in spite of frequent aspirations and use of formalin and glycerine. On May 13, we inserted two catheters between the ribs. Irrigation every two hours with Dakin's solution and anilin dyes, as well as autogenous vaccines were all tried. After a year in bed the drainage continued and constitutional symptoms were still present. Under local anesthesia the 10th, 9th, 8th, 7th and 6th ribs were completely removed. A few weeks later the drainage had ceased and the patient was again symptom-free. Soon after this he went to work and is now apparently in good health. We evidently infected this patient. This is our only case of mixed infection, though we have had several tuberculous empyemas complicating artificial pneumothorax.

Case 6: J. E. M. Age 40, merchant, admitted September 23, 1918, with advanced symptoms and dense tuberculous infiltration of entire left lung, with less dense changes in right upper. Sputum Gaffky VI. Artificial pneumothorax was attempted, but unsuccessfully. Thoracoplastic operation was advised and refused. Patient left the sanatorium six months later, having shown little improvement. Temperature was 102° daily, and other symptoms unabated, though he had gained 5 pounds. Patient remained at strict bed-rest for almost three years and again returned for a few weeks' observation January 16, 1922. Physical and X-ray findings little changed though patient's general condition was markedly improved. Following this, spent two months at Saranac Lake where thoracoplasty was again advised. He returned in December and at this time presented general appearance of

health, but continued to have flareup of cough, expectoration and fever, and could acquire no endurance. The first stage of the posterior operation was done under local anesthesia, removing sections of 5th to 10th ribs inclusive. Following this he was practically symptom-free for 15 months. We again saw him March 14, 1924. At this time temperature and pulse were normal, he was overweight, but claimed to have lost some of his endurance; cough and expectoration increased. Resection of the remaining four ribs was advised. Though he has at this time a fairly satisfactory basal collapse, the 11th rib should have been cut. The opposite lung is holding up well and his chances for getting on his feet again appear good.

Case 7: Mrs. J. T. K. Housewife, age 32, admitted April 29, 1923. Patient gave history of having had tuberculosis for eight years, and had been in several sanatoria, both in East and West. Physical examination revealed, on right, dulness throughout, most marked at base. Breath sounds bronchial at base, posteriorly, and cavernous in 3rd and 4th interspaces in anterior axillary line. Subcrepitant râles on deep breathing and following the auscultatory cough throughout front and back. On left, crepitant râles were heard to *R 4* and *5 d.s.* Sputum Gaffky VIII; blood pressure, 90–60; stereo-X-ray report as follows: *Right Lung:* Slight mottling with numerous areas of calcification to *R 3* and *7 d. s.* From this point to diaphragm there is dense mottling, with area of lessened density interpreted as cavity (3 cm. in diameter) near periphery, back of 3rd rib and 3rd interspace, using anterior markings. *Left Lung:* Some fibrosis to *R 4* and *8 d. s.* Artificial pneumothorax unsuccessful. In May her condition had become extremely critical, the temperature reaching 104° daily and at times there were periods of delirium. Under local anesthesia, the 4th to 11th ribs, inclusive, were resected (posterior operation). Within 48 hours the temperature was normal and she had practically no cough and expectoration. Five weeks later she informed me that she was well, and left the sanatorium. At this time the cavity was shown by X-ray to be completely obliterated. The cavity being basal explains the brilliant immediate results from this operation. Have recently heard that the patient was dead, but cannot learn the particulars. With continued coöperation from the patient I feel that the ultimate outcome might have been different.

Case 8: Mr. C. R. Druggist, age 25, admitted May 2, 1920, from another sanatorium where he had been a bed patient for over a year. Physical examination revealed moisture throughout left lung. Right was negative except for impaired resonance to *R 2* and *5 d. s.* Stereo-X-ray showed "cotton-ball" mottling throughout left and fibrosis of upper right. Profuse and persistent hemoptysis, coupled with the fact that there had been no improvement after twelve months bed-rest in a sanatorium, prompted us to

collapse his left lung July 23, 1920. Satisfactory basal compression was accomplished, but apex was firmly adherent to *R 2* and *5 d. s.* In spite of this there was almost immediate cessation of bleeding and marked general improvement. For over a year the patient was symptom-free, but in June, 1922, cough and expectoration reappeared and he began to lose ground. Physical and X-ray examinations at this time disclosed a cavity in the uncompressed apex. Several months' bed-rest did not ameliorate the symptoms, and moisture appeared in the right apex. Severe gastrointestinal upsets made it necessary to remove a chronic appendix under local anesthesia in September, 1922. In September, 1923, under local anesthesia, the 4th to 9th ribs were cut (posterior operation). But for troublesome effusion, apicolysis, according to Archibald, would have been the operation of choice. We expected to complete the second stage of the operation a few weeks later and anticipated practically no results from the first stage. There has been marked improvement, and his general condition is more satisfactory than it has been since onset of illness. His only symptoms are slight cough and expectoration in early morning. He is a small-boned, thin-chested man, and there has been notable caving-in of the upper chest also, and this grows more marked as time elapses. It seems probable that in this instance, nature will make the second stage of the thoracoplasty unnecessary.

We are profoundly conscious of our paucity of experience in this work as compared with that of many. We are also sensible of the fact that our report of cases shows no particular brilliance in results; neither do they present anything new. From them we feel that we have learned much that will enable us to better select the type of operation most suitable for the individual case. The object of this paper will have been largely attained, if it serves in any way to imbue those treating tuberculosis with some of our enthusiasm. We also believe that from a careful persual of the splendid work being done by Archibald, Lilienthal, Eloesser and others, combined with our own limited experience, we are able to arrive at some definite conclusions.

CONCLUSIONS

1. Phthisotherapeutists as a whole are not alive to the aid which chest surgery, in the treatment of certain cases of heretofore hopeless tuberculosis, offers. This is evidenced by the fact that Archibald, the real pioneer of this work in this country, reports less than 50 cases of extrapleural thoracoplasty. In a modest practice during the past ten years we have failed to collapse, by artificial pneumothorax, 38 out of 117 cases

attempted. Since 20 of those collapsed have, for the present at least, been rehabilitated, and many more have had their lives prolonged and made more bearable, it would seem reasonable to conclude that of those now dead thoracoplasty would have probably restored a few to useful citizenship.

2. The ultimate success of this work depends primarily on the tuberculosis specialist. He should select the case and, with the surgeon, the type of operation, since it is he who treats the case for months thereafter and thereby naturally has better opportunities for studying end-results. To quote Lilienthal: "The surgeon must never lose sight of the fact that, although his wound may heal and his immediate objective be reached, his patient still has tuberculosis and will long require medical and hygienic treatment."

3 Thoracoplasty should not and cannot supplant artificial pneumothorax, since the latter allows a return of function to the diseased lung.

4. The posterior operation, resection from the 1st to the 11th ribs inclusive, will in most cases accomplish sufficient collapse. The lower eight or nine ribs can be cut practically painlessly under local anesthesia, with, if necessary, gas-oxygen for the upper two or three. This has proved far superior to the old Sauerbruch method with its high operative mortality.

5. While, as a rule, all of the ribs must be cut, to allow the necessary collapse, in certain thin-chested, small-boned patients, a surprising caving-in of the upper uncut ribs will gradually take place, especially when compression bandages are applied over a long period of time (case 8).

6. With apical cavities and functionating bases, apicolysis, by pectoral-muscle implantation, according to Archibald, or fat transplantation, as used by Lilienthal, is superior to artificial pneumothorax. Either one or both apices can be collapsed. When the densest pathological process is basal, with little if any upper-lobe involvement, a condition that is not so infrequent as many would have us believe, posterior resection of eight or nine lower ribs may be sufficient to relieve the symptoms, and in such a case it presents certain advantages over pneumothorax.

7. Tuberculous empyema only too often seriously complicates artificial pneumothorax; when other treatment fails to collapse the lung thoracoplastic collapse should be done.

8. Intrapleural pneumolysis and maintenance of compression are often not so simple as they may seem. If there has been much lung destruction, thoracoplasty is often the most simple and logical procedure.

In conclusion, I would again appeal to the tuberculosis specialist to avail himself of the indispensable services of the surgeon in treating certain selected cases of otherwise hopeless tuberculosis. The phthisiologist and the tuberculous sick owe a debt of gratitude to the many great surgeons who have put and are still putting forth every effort to simplify the operation and are making its use more generally feasible. We wish especially to express our appreciation of Dr. Archibald, who has, in personal communications with Dr. S. S. Gale, the operator in the reported cases, offered much invaluable advice and constructive criticism.

Note: Since writing the above we operated on a left-sided case, in which we had every reason to expect good results. All but the upper two ribs were cut at one operation. The following day the patient developed dyspnea and a rapid pulse; two days later moisture appeared in the contralateral lung, and he died on the ninth day. This patient died because in our enthusiasm we overestimated his endurance and did too much at one operation.

TOTAL PARALYSIS OF THE HEMIDIAPHRAGM FOR EARLY PULMONARY TUBERCULOSIS[1]

JOHN ALEXANDER

Failure of strict sanatorium regimen to check the progress of a not inconsiderable number of cases of early pulmonary tuberculosis is responsible for the recent increasingly favorable reception of the proposal that artificial pneumothorax should frequently be used for initial lesions that do not give reasonable promise of an entirely satisfactory response to routine treatment. Were it not for the high percentage of complications and dangers that artificial pneumothorax entails, undoubtedly this suggestion would have been put into practice long ago. The indisputably favorable results obtained during the past three years by totally paralyzing one-half of the diaphragm in moderately advanced and far advanced tuberculosis leads me to suggest its use for those *early* cases in which artificial pneumothorax would be indicated were complications not feared, and if both patient and physician did not hesitate to begin a course of tedious treatment that ought to be continued for one year at the very least. Phrenicotomy is without noteworthy danger to the patient and in this respect is distinctly superior to artificial pneumothorax. Functional respiratory impairment is negligible.

Simple section of the phrenic nerve in the neck was proposed in 1911 by Stuertz as treatment for basal tuberculosis, especially in the presence of cavitation. In 1913 Schepelmann suggested its use for early pulmonary tuberculosis. Clinically, very little was done with this proposal until 1921, when Goetze and Felix, after extensive laboratory and clinical research, found that in 25 per cent of cases the diaphragm did not stay completely paralyzed after simple phrenicotomy because accessory motor fibres, entering the main stem below where it is conveniently sectioned, remained intact. Each investigator proposed a "radical phrenicotomy" operation that would interrupt all motor fibres to the diaphragm (except a few unimportant ones from the twelfth intercostal nerve). Of the two procedures Felix's *phrenicus-exairesis*, a twisting out of the upper portion

[1] From the Department of Surgery, University of Michigan Medical School.

of the phrenic nerve, has gained the greater favor; I have described its technique in a recent article (see bibliography). It is strictly a minor operation, performed in a few minutes under local anesthesia, and leaves only a five or six-centimetre-long transverse scar, hidden in a natural skin fold in the posterior triangle of the neck. As a result of this operation the hemidiaphragm becomes completely atonic and rises into the chest, where it remains motionless or subject to very slight paradoxical movements.

Felix found that the differences in height between the paralyzed and unparalyzed sides of the diaphragm are 7 cm. at the end of inspiration and 3 cm. at the end of expiration; the figures given are averages, and would be a little greater when the right side is paralyzed, a little less when the left is paralyzed. Sultan has seen a paralyzed right diaphragm 11 cm. higher than the left, and another case in which a paralyzed left side (normally 2 cm. lower than the right) was 9 cm. higher than the right. Felix found, experimentally, a reduction in the capacity of the right hemithorax of from one-sixth to one-third, and even more; this is only very slightly less than is obtained with a Sauerbruch paravertebral thoracoplasty. The effect, then, of radical phrenicotomy is the marked curtailment of the respiratory activity of a hemithorax, and a diminution of the capacity of that side of the chest, causing a relaxation of the lung. It is probable that the relaxation is greater in the lower than in the upper lobe, amounting to a partial compression; but in the absence of pleural adhesions in the lower chest this relaxation is shared by the entire lung and is greatest where elastic tension (shrinking tubercles) is greatest, and therefore the relaxation is selective. Zadek has seen very marked improvement in an upper-lobe cavity. It is apparent that diaphragmatic paralysis would have little or no influence in effecting rest and relaxation of an upper-lobe lesion if the lower or middle lobes were involved in pleural adhesions; therefore physical evidence of such adhesions, or presumptive evidence based upon a history of exudative pleurisy, would contraindicate phrenicotomy for upper-lobe lesions. Adhesions over the apex would hardly contraindicate it, as they would further the pulmonary rest, even though they would hinder, to some extent, the relaxation.

Radical phrenicotomy has been found of great use in a number of tuberculous conditions, as well as for diaphragmatic tetanus, persistent singultus, for some operations upon or in the neighborhood of the diaphragm, and for certain cases of lower-lobe bronchiectasis and of chronic empyema

cavity. When performed for tuberculosis the lesions should be predominately unilateral, but as only a very little, if any, extra work is thrown upon the lung of the opposite side under normal conditions of life, this reservation need not to be as strictly observed as for artificial pneumothorax, and far less strictly than for extrapleural thoracoplasty.

The operation has been found serviceable for tuberculosis under the following circumstances:

I. INDEPENDENT OF ARTIFICIAL PNEUMOTHORAX OR EXTRAPLEURAL THORACOPLASTY

A. In acute, highly febrile, progressive, predominately caseous types of the disease, even when there is considerable activity in the better lung and in which artificial penumothorax and extrapleural thoracoplasty are contraindicated. Some startling results have been obtained with such cases.

B. For the less acute types of disease, in which pneumothorax cannot be induced because of adhesions, or in which thoracoplasty is feared because the patient's general condition is too poor, or because the better lung is too much diseased.

C. For those cases in which no contraindications to artificial pneumothorax or thoracoplasty exist, but in which phrenicotomy might be expected to effect as good results, and without the prolonged treatment and dangers of the one, and the hazards of the other. Goetze, Hans Alexander, Fischer and Frisch are alone in advocating it under such conditions.

II. SUPPLEMENTARY TO ARTIFICIAL PNEUMOTHORAX OR THORACOPLASTY

A. When partial or total pneumothorax is not producing satisfactory results: (a) together they may check the disease and make a thoracoplasty unnecessary; (b) especially in basal disease, which is always grave and requires the greatest and longest possible rest and compression (Maendl); (c) when adhesions of the lower lobe to the diaphragm are causing pain, irritating unproductive cough, vomiting or indigestion (Lehmann adds phrenicotomy to pneumothorax in every such case); (d) when it is feared that the lung may creep out under an effusion and adhere in the expanded position; (e) for persistent hemoptysis that pneumothorax has not succeeded in checking; several successful cases have been reported.

B. Supplementary to a complete or entirely satisfactory artificial pneumothorax: The diaphragm is but little hindered from rising into the thorax by the higher intrapleural pressure of the pneumothorax. It is my belief that the time will come when almost every artificial pneumothorax undertaken in the best clinics will be preceded or followed by a radical phrenicotomy. Brunner considers such practice inadvisable because there is a

certain small percentage of patients in whom artificial pneumothorax later becomes indicated for the originally better lung. The principal advantages to be gained are: (a) When the pneumothorax is finally released at the conclusion of the treatment, the shrunken fibrotic lung will need to expand only to fill a cavity that has been proportionately reduced in size, and not one that is so much bigger than the lung that the walled-off tubercles and closed cavities would be tugged at and torn open. The lessened respiratory activity of the hemithorax is further insurance against reactivation of the disease when the patient resumes active life. (b) Frisch and Sauerbruch find that the pneumothorax needs to be refilled much less frequently after the diaphragm has been paralyzed. Frisch reports a case in which the intervals were lengthened from three to four weeks to seven to twelve weeks. (c) Sauerbruch and Zadek report fewer and smaller effusions when phrenicotomy and pneumothorax are combined than when pneumothorax is used alone. (d) In case the patient permanently abandons the artificial-pneumothorax treatment the high immobile diaphragm will forever serve as a partial substitute for the total compression of the abandoned pneumothorax, and may be sufficient to maintain the gains already made.

C. Supplementary to extrapleural thoracoplasty: Stöcklin, Hans Alexander and the Sauerbruch Clinic recommend phrenicotomy with almost every thoracoplasty. Its special indications in this connection are: (a) To cause sufficient improvement in a sick patient to make later thoracoplasty a safe undertaking. (b) When the heart and trachea have been drawn far to the diseased side, or when conditions named under *II A* (*b*) or (*c*) are present. (c) To relax a clinically undiseased lower lobe in order to prevent its aspirating the secretions pressed out of the diseased upper lobe at the time of a thoracoplasty limited in extent to the upper ribs. (d) Sauerbruch frequently performs phrenicotomy to determine whether or not suspicious lesions in the better lung are actively tuberculous. He believes that a paralyzed raised diaphragm causes sufficient increased respiratory activity in the opposite lung temporarily to activate any latent lesions there. If no activity were demonstrable clinically, in three weeks he would consider thoracoplasty safe; otherwise he would not at that time, but would wait to see what improvement the paralyzed diaphragm would cause in both lungs. He does not fear that this mild activation of lesions in the better lung will be permanent. As unilateral paralysis of the diaphragm does not cause any noteworthily demonstrable increase in respiratory activity of the opposite side of the chest it would seem that the appearance of fresh activity in any lesions of the opposite lung had better be attributed to an excess of toxins ("over-tuberculinization") being pressed out of the more diseased lung into the general circulation by the risen diaphragm.

The great majority of those familiar with the use of phrenicotomy in tuberculosis (moderately advanced and far advanced forms) advocate its

use only in conjunction with artificial pneumothorax or thoracoplasty. Too many variables and too few reported cases conforming to any one group of conditions make a consideration of statistics almost useless. A study of the published individual case histories will alone yield, at the present time, satisfactory information. However, Goetze has reported more than 50 per cent of improvements and many "healings" after radical phrenicotomy used alone, and Fischer reports even better results in severely diseased patients.

Although phrenicotomy alone, without the supplementary use of pneumothorax or thoracoplasty, cannot be advocated as a routine curative measure in moderately advanced or far advanced largely unilateral tuberculosis, it has demonstrated its ability greatly to improve, and in some cases even completely to arrest, these severe forms of the disease. It follows as a logical deduction that, when used in conjunction with adequate hygienic management, it may be expected to assure clinical cure in many of those cases of early tuberculosis in which the balance between health and disease is notoriously even, but in which sanatorium treatment alone is by no means always able to weight the scales in favor of permanent health. My suggestion for the extensive use of phrenicotomy in such cases has two further advantages. First the "curing" time would probably be decidedly shortened (an economic asset of no mean importance!), and second, the ultimate, as well as the immediate, prognosis would be better for the reason that the capacity of the chest would be lessened to correspond with the lessened size of the healed and shrunken lung, and because any unusual respiratory demands would argely be met by the undiseased lung. By virtue of the permanent paralysis of its diaphragm the "healed" lung would never be put under great strain.

Physicians not familiar with phrenicotomy may express tentative doubts as to the safety of the method, and fears of functional respiratory disability. Felix's radical phrenicotomy is known to have been performed 240 times without a single serious accident; 150 of these operations were done at Sauerbruch's Clinic. The rare minor operative complications that have been met with were caused by firm adhesions or caseous tubercles close to the phrenic nerve in the superior mediastinum, but such lesions would not be present in the early cases. Instead of making expectoration more difficult, phrenicotomy makes it easier, because even though the tidal air is less, the lax diaphragm offers no resistance in the expulsive effort of the powerful abdominal muscles. Paraly-

sis of one-half of the diaphragm does not cause noteworthy respiratory embarrassment; even should the lung of the opposite side be attacked by pneumonia it is possible that the costal respiration of the paralyzed side could compensate. Bilateral phrenicotomy has been performed a number of times for persistent singultus or to prepare for artificial respiration in diaphragmatic tetanus, and the resulting dyspnea was only temporary (Sauerbruch, 1920). If for any reason, for example, a questionably progressive tendency of any lesion in the better lung, it might seem preferable that the diaphragmatic paralysis should not be made permanent, 70 per cent alcohol may be injected into the main phrenic stem (Goetze), or it may be frozen with ethyl chloride (Balderrey), or with a tube of ice (Fischer), or, less advisedly, simply sectioned and sutured, and a return of function may be expected in about four months (Kroh); then, if the effect of the paralysis has been satisfactory, the definitive operation should be performed. I have made experiments upon dogs (as yet unpublished), which show that diaphragmatic paralysis does not produce pleural adhesions (observations up to six months) that might prevent the induction of an artificial pneumothorax, should it become advisable, nor, as Maendl has shown, does a therapeutic pneumothorax of the usual intrapleural pressure much depress the diaphragm.

CONCLUSION

The decidedly favorable influence of the pulmonary rest and relaxation caused by complete paralysis of a hemidiaphragm in advanced tuberculosis strongly supports the suggestion that radical phrenicotomy, in conjunction with usual careful hygienic regimen, would offer to patients with predominately unilateral *early* tuberculosis, who are not making satisfactory progress under the hygienic regimen alone, a greater chance of early and permanent clinical cure than any other known method of treatment. It is deserving of trial.

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LIGATION OF THE PULMONARY ARTERY COMBINED WITH RESECTION OF THE PHRENIC NERVE IN CHRONIC INFLAMMATORY CONDITIONS, ESPECIALLY TUBERCULOSIS OF ONE LUNG[1,2]

KARL SCHLAEPFER

Chronic inflammatory conditions of the lung are the result of a long-standing, continuous fight of the body against an invasive infection. The onset may be an acute process that becomes chronic because of a lowered resistance of the body, or the infectious process is insidious from its very beginning and stays so for years. Because of its great frequency and infectious character for man tuberculosis is probably the most important of those conditions that deserve the greatest attention.

In this article only cases of unilateral tuberculosis will be considered. The number of cases in which even a very advanced lesion remains limited to one side is not so small, if one considers the total number of cases of pulmonary tuberculosis. Bronchiectasis, lung abscess, actinomycosis and anthrax are other conditions of the lung which, in some cases, are also restricted to one side and become then available to the surgical procedures to be discussed in this contribution.

It is a characteristic feature of pulmonary tuberculosis that nature tries to isolate the focus of infection within a fibrous envelope, thus cutting off the connection between host and invader and making the focus quiescent. Hygienic and climatic measures, combined with complete rest, bring about an increase of the general resistance, and through this favor also the physiological reaction in the diseased lung by way of an increasing fibrosis.

Various additional surgical procedures have been advised to put the diseased lung temporarily (artificial pneumothorax) or permanently (extrapleural thoracoplasty) at rest, to facilitate the course of healing. The aim of this paper is to discuss a new procedure, based on a series of experiments on dogs, together with some clinical experiences along the same line which seem to offer bright prospects of being able to produce

[1] From the Surgical Department of the Johns Hopkins University and Hospital.
[2] Read before the Interurban Clinical Club, Baltimore, March 16, 1923.

surgically a denser fibrosis around the focus within a relatively short time, and thereby guarantee a clinical cure of certain forms of unilateral tuberculosis hitherto only temporarily benefited after prolonged treatment.

1. MEDICAL TREATMENT SUPPLEMENTED BY ARTIFICIAL PNEUMOTHORAX

The bases of any treatment of advanced unilateral tuberculosis are the hygienic-climatic measures; but for more advanced cases, now under consideration, this treatment is generally not sufficient, the lung being forced to continue its strenuous work and therefore unable to combat successfully the infection. The specific inflammation increases in this way, extending in the one affected lung and sooner or later spreading to the other side also.

Very early (Carson 1822, Ramadge 1834) attempts were made to put the diseased lung at physiological rest by an artificial pneumothorax. Forlanini (1882), and in this country Murphy (1898), began systematically to use this form of treatment in selected cases. Brauer (1904) worked out the underlying physiological and anatomo-pathological changes occurring within a lung collapsed by artificial pneumothorax. For a longer period of time (1–2 years) the diseased lung is forced to inactivity by a complete collapse. A chronic stasis is present in this lung, with a reactionary fibrous tissue growth which augments the fibrosis arising as a reaction to the infection. The hygienic regimen has to be kept up for the duration of the treatment, until the foci of infection become quiescent. This takes generally one to several years, the lung being capable of resuming work after this lapse of time, by abolishing the pneumothorax.

Artificial pneumothorax therapy is practicable only in cases in which the pleural cavity is not greatly obliterated by widespread adhesions that result from pleurisy which is so frequent in pulmonary tuberculosis. If these adhesions are not too extensive they can be broken up and the partial pneumothorax transformed into a total one, the only efficacious form of this therapy. Jacobaeus advised thoracoscopy (endoscopy) and cauterization by which these adhesions could be burned off. It has been found suitable in only a few exceptional cases which would be benefited perhaps in a safer manner by artificial pneumothorax with increased pressure.

2. EXTRAPLEURAL THORACOPLASTY

When the adhesions are too dense and diffuse, extrapleural thoracoplasty is indicated. The rigid chest wall of the affected side is mobilized, and thus the lung is brought to a collapse (taking away segments from all ribs). This was done in a very radical way by Brauer and Friedrich, through partial resection of all ribs by multiple rib resections over the whole affected side. It was a modification of the thoracoplasty used for years with success in cases of chronic empyema (Estlander, Schede). A total collapse was the aim of this therapy, giving, as proved by Brauer, the best results. Sauerbruch worked out his paravertebral method, using an angular incision posteriorly in the paravertebral line and resecting, generally in one or two stages, pieces of the eleventh to first ribs, varying in length with the degree of the underlying pathological lesion. This method guarantees a complete collapse in a vertical but not in a horizontal plane. Wilms's *Pfeilerresection* took pieces 3 to 4 cm. long from the first to eighth ribs posteriorly. Three weeks afterward the rib cartilages were cut at their insertions at the sternum. This method gives no complete collapse in either a horizontal or a vertical plane. It is now completely replaced by Sauerbruch's method.

Judging from the experiences obtained with artificial pneumothorax, a complete collapse of the diseased lung was postulated as the aim of any thoracoplasty, thus guaranteeing a complete physiological rest of the organ. By this procedure there was practically a complete suppression of air exchange, the foci of infection not being put to a stretch at every inspiration. Then too, this facilitated the contraction of the organ, secondary to the reparatory fibrosis, which was previously hampered by extensive pleural adhesions.

In the endeavor to meet all these conditions Brauer worked out his subscapular-paravertebral method, resecting the ribs from the first one down to the eleventh, in an area from the anterior axillary line backward to the line of the transverse vertebral processes; the scapula is a great aid for obtaining a total collapse of the lung. This method is applicable to more advanced cases in which only the complete collapse provides a good result. Sauerbruch's less efficacious method gives also very good results in suitable cases, as depicted later when reviewing the statistics of the different operators.

A. Action of these procedures on the lung

By measures acting indirectly, compressing the lung from the outside, either by interposing gas between the lung and the thoracic wall, or by mobilizing the rigid chest wall by extensive rib resection, the diseased organ is forced to a collapse.

A stasis results in the pulmonary circulation with an increased blood volume as demonstrated by Cloetta. All the capillaries become dilated. They seem to show an increased permeability. The resulting edema is counteracted at the beginning by an accelerated lymph-flow (Shingu, Brauer, Bruns, Kistler). The chronic stasis in the pulmonary circulation is responsible for the proliferation of the adventitial tissue of the arterioles and capillaries. It is a process analogous to that observed in any parenchymatous organ (liver, pancreas, kidney) in the stage of chronic congestion. This fibrosis is added to the fibrous envelope resulting from the reaction around the foci of infection, which is particularly characteristic of chronic tuberculosis. Cavities in a tuberculous lung collapse when these additional surgical measures are used. The expectoration is facilitated, thus diminishing its absorption by the body. As demonstrated by Le Blanc, after one-sided lung collapse a slight deficit of the oxygen saturation in the systemic blood occurs, proving that unarterialized blood passes through the collapsed lung and is mixed with the greater amount flowing through the intact side. This does not contradict the assumption made by Sauerbruch and Cloetta that a chronic stasis takes place in this lung. The resulting fibrosis is an objective proof of this fact.

B. Results with additional artificial pneumothorax and extrapleural thoracoplasty

Only a relatively small number of the suitable cases were submitted to one of these two additional treatments to hygienic-dietetic measures. The places where this treatment is performed were restricted until recently to Switzerland, Germany, France and Northern Europe. Even with this aid a considerable length of time is necessary for a clinical cure. This means a great economic sacrifice for the patients or the authorities whose broadmindedness allowed the creation of these special places. They form a further step in the successful fight against tuberculosis in the community.

Lucius Spengler (Davos) followed up 88 patients treated with artificial pneumothorax; 23 (26 per cent) were clinically healed. They remained well also after resorption of the air in the pneumothorax. Thirty-six (41 per cent) were improved; but they still remained under treatment. Nineteen (21.3 per cent) were not benefited by artificial pneumothorax.

Sauerbruch (Munich-Zürich) performed his thoracoplasty on 169 cases in one stage: 23 (13.6 per cent) died within the first three weeks after the operation; 38 (22.5 per cent) died from seven months to seven years afterward. They were improved for a variable length of time. Definitely improved were 41 (24.4 per cent); cured ($1\frac{1}{2}$ to 6-years' observation) were 61 (36.1 per cent). Six did not answer the questionnaire. When the operation was performed in two stages, the immediate mortality was lowered. Of 54 cases 6 died within three weeks from the time of operation (11 per cent). The percentage of cures was greater, being 23 (43 per cent); 6 (11 per cent) were much improved.

Bull (Christiania) reported 75 cases of extrapleural thoracoplasty, using a method similar to Sauerbruch, by resecting through a paravertebral incision, posteriorly, pieces from the eleventh to first ribs inclusive. Eight died sooner or later as a result of the operation (10 per cent). Sixty-four were observed for more than one year and up to eight years. Thirty-eight (59 per cent) of these were still alive without symptoms. Nine were tuberculous, and in four the result was undetermined.

Brauer (Hamburg-Eppendorf) reported the following results with his subscapular-paravertebral method: 30 per cent cures, 30 per cent considerable improvement. Brauer emphasizes the fact that he submitted to this operation only very advanced cases of unilateral tuberculosis which would have been lost with purely medical treatment. Extensive obliteration of the pleural cavity by dense adhesions made the use of an artificial pneumothorax in these cases impossible. Twenty to 25 per cent of the cases did not improve after the thoracoplasty; 10 to 15 per cent became worse because of the activation of a tuberculous process on the nonoperated side. As to the advisability of a thoracoplasty, phrenicotomy on the side of the intended thoracoplasty (Sauerbruch) would have proved or disproved its feasibility.

These data illustrate the efficacy of these surgical measures in carefully selected cases. Clinical cure or at least great improvement is obtained in unilateral pulmonary tuberculosis, which would gradually go the usual course with medical treatment alone, and finally die. One of their

shortcomings which stimulated my experimental investigations was the long time necessary for these results. In a disease of such great frequency among all classes of the population, it would be of greatest industrial (economic) importance to shorten the time of complete rest for these patients during which it is necessary to stay away from their usual occupation. In performing these experiments, I took up the work of Küttner, Bruns and Sauerbruch, and Robinson. I employed a method which I hope will be more efficacious in a larger percentage of cases than had hitherto been suitable for surgical treatment. A few clinical cases recorded in the literature (W. Meyer, Sauerbruch) and others quoted in a subsequent chapter (v. Voornveld-Wilms) seem to substantiate my assumption and at least justify more exhaustive investigations.

3. EXPERIMENTAL PART: LIGATION OF THE PULMONARY ARTERY WITHOUT AND WITH RESECTION OF THE PHRENIC NERVE

The following experiments are intended to lay down some rules governing the anatomy and physiology of a method which puts the lung at rest by direct action. The method comprises ligation of the pulmonary artery. In a parallel series I combined the ligation with paralysis of the diaphragm on the same side.

1. Physiological changes

By ligation of the pulmonary artery, we cut off the venous blood supply that is to be arterialized in the lung. The intact bronchial artery guarantees sufficient blood to prevent the formation of an infarct, although the circulation is greatly impaired during the first eight to ten days, a stasis being the prominent feature; later a certain adaptation to the new conditions takes place, the stasis still persisting and becoming chronic. Ligation is tolerated without any marked alteration of the rate of the heart beat or respiration. This was conspicuous in our experiments, but is also reported by the surgeons (W. Meyer, Sauerbruch, Wilms, Garré) in their clinical cases. Immediately after ligation of the pulmonary artery the blood pressure in the one remaining pulmonary artery rises about 40 per cent, as was demonstrated by Underhill, and stays up for about one-half hour. This is the time necessary for the other lung to take over the whole respiratory function. By dilatation of all the capillaries the peripheral resistance in this lung is diminished

and an increased velocity of the blood sets in, thus guaranteeing a normal oxidation of the blood. Deepening of the respiration with slight slowing of the rate per minute increases the respiratory exchange of the lung. An increase in the rate was perceptible in our cases with a deepening of each breath, partly as an effect of the pain due to the wound. The right heart pumps out the same amount of blood with each contraction after ligation, as proved by Lichtheim and Tigerstedt in estimating the blood-volume passing through the lesser circulation. This insures a normal arterialization of the blood by the one functioning lung. The elevation of the blood pressure in the pulmonary artery immediately after ligation was, in our experiments, probably the cause of death in rabbits, the pressure becoming also higher in the right heart. Dogs usually stand this change better. Drinker, Peabody, and Blumgardt showed that this elevation becomes deleterious if surpassing a certain level.

With the rise of pressure in the lesser circulation, we observed a slight fall in the systemic circulation (femoral artery) as demonstrated with a plethysmographic method by Dr. Kolls of the Physiological Department of the Johns Hopkins University. This is present only for a short time (15 to 30 minutes); afterward the blood pressure returns to its normal level. This fall is explained on the basis of a deficit in the greater circulation resulting from the blood stored in the ligated lung. This difference probably is balanced by reflex contraction of vessels, perhaps in the splanchnic area. These immediate effects of ligation are about the same after ligation alone or when combined with paralysis of the diaphragm, the fall in pressure in the systemic circulation being perhaps more marked in the second condition because of the greater stasis in the ligated side.

The hyperemic intact lung has the tendency to expand, as demonstrated in the subsequent findings of our experiments. This expansion is an effect of the dilatation of all the capillaries outlining the air sacs. As shown by v. Basch, coils of rubber tubing filled with water and wound around a rubber bag, bring this bag to expansion when the water content in these tubes is increased, and simultaneously the tubes also dilate. The same action becomes effective in the one functioning lung after ligation of the pulmonary artery of the other side. The dilatation becomes more and more pronounced, affecting, after three months, even the larger branches of the pulmonary artery.

Experimentally, we obtained the same enlargement when we injected a nonpermeable fluid into the pulmonary artery of a lung (bismuth-

gelatine suspension). Microscopically, the enlargement of all the alveoli was very conspicuous. The compensatory hypertrophy in these cases is probably due only to this secondary dilatation of the alveoli and not to new formation of alveoli. The dilated lung pushes the mediastinum with the heart toward the operated side, thus exerting a gradually increasing pressure on the ligated lung. When the diaphragm was paralyzed, the operated lung became also more and more compressed by the increasing elevation of the diaphragm.

2. Anatomic changes

The dogs were very lively after the first 24 to 48 hours, during which they were suffering from the shock of the operation. No thoracic deformity was noticeable after this time, probably because of the lack of extensive pleural adhesions, as was observed in analogous cases by Bruns, Sauerbruch, and Kawamura. In our series pleural adhesions were restricted to places of traumatism at the time of operation; along the mediastinal side, when performing the ligation, and in some cases at the line of incision on the anterior chest wall. The remaining portions of the pleura were smooth, glistening and free, showing that there was no inflammatory reaction, due to postoperative oozing or avoidable handling at the time of operation. The X-rays showed no greater intercostal expansion on the intact chest side, to indicate increased expansion of this lung.

Two factors resulting from these surgical procedures were followed during life by a series of X-rays and were subsequently verified in detail by necropsy: (1) the gradual displacement of the mediastinum with the heart; and in cases in which the phrenic nerve was resected, (2) the gradual elevation of the paralyzed diaphragm (fig. 1).

As seen in figure 2 the expanding intact lung pushes the anterior mediastinum with its medial borders to the side of ligation. This takes place within the first few days after the operation and increases gradually. Thus hollows are formed in the weak places of the anterior mediastinum, above the heart, and below and anterior to the pericardium. The heart is also pushed toward the operated side, this being not so conspicuous in all specimens to the same extent. A change, illustrating very well the expansion of the intact side, is the enlargement of the right mediastinal lobe when ligation of the left pulmonary artery was performed. This lobe, normally situated behind the pericardium, extends in these cases

away over to the left lateral thoracic wall (fig. 3.). This shows very well the compensatory hypertrophy of the intact lung. This lobe gradually becomes situated between the left lung and the left diaphragm. The resulting reduction in size of the lung after ligation alone is depicted by figures 4a and b. Since we have only the mediastinum as a compressive agent the reduction is only a relative one in this early stage as compared to the subsequent series with paralysis of the diaphragm.

When the diaphragm was paralyzed by phrenic resection a second factor became active and proved to be very effective; namely, the increasing elevation of the diaphragm due to indirect compression by the muscles of the abdominal wall through the action of the abdominal contents. This is a very helpful factor in compressing the lung put to rest by ligation of the pulmonary artery. Figures 5a, b, and c illustrate very well the action of the mediastinum, and particularly that of the diaphragm. With phrenicotomy, the apex of the heart is elevated through this rise of the diaphragm. The atrophy following this phrenic resection was a unilateral one with sharp demarcation in the middle line, proving that the phrenic is the only motor nerve for the diaphragm. Electrical stimulation experiments endorsed this view which is published in an article in the *Bulletin of the Johns Hopkins Hospital.*

In a parallel series the phrenic was not resected, but was crushed for a distance of 2 cm., the anatomic continuity of the sheaths being maintained. For $2\frac{1}{2}$ to 3 months the relaxation of the diaphragm was a complete one, the degree of elevation being the same as after resection. Later the tonus gradually returned, and at $4\frac{1}{2}$ months both sides of the diaphragm showed the same degree of contraction.

An illustration of the circulation in the lung, with the pulmonary artery ligated, is given by the changes noted in the size of the bronchial artery, the main nutritive vessel of the lung, which, after ligation of the pulmonary artery, takes up a continuous circulation into the pulmonary veins and the left auricle. In dogs this is facilitated by the fact that the pressure in the bronchial artery is about four times higher than in the pulmonary artery. At the end of the first week after operation this blood-flow becomes very effective and diminishes, to a certain extent, the stasis in the lung. As a result of this increased circulation, a marked enlargement of the calibre of the bronchial artery is noticeable within two months following ligation alone and within three months after ligation combined with resection of the phrenic nerve (fig. 6). This difference in time is proof of the pumping action of the diaphragm, rendering

easier the blood-flow through the normal lung, and demonstrating an analogous action on this altered circulation in the ligated side. The paralyzed diaphragm makes it rather difficult for this bronchial-pulmonary circulation to become effective, the stasis in this lung being more marked for a longer time than after ligation alone.

Another result of the longer persisting extreme stasis after paralysis of the diaphragm combined with ligation of the pulmonary artery is a marked contraction of the wall of the pulmonary artery distal to the place of ligation; the latter is first noticeable after three months. Following ligation without phrenicotomy it is visible after two months.

The microscopic picture is a further proof of the gross anatomic findings. It explains at the same time the physiological changes occurring after ligation of the pulmonary artery without or with resection of the phrenic nerve.

On the intact side, dilatation of all the capillaries is characteristic, becoming rather more pronounced after months (fig. 7). The tortuous dilated vessels in the alveolar walls are striking. No sign of fibrous-tissue proliferation is visible. The elastic tissue is not increased, either around the capillaries or in the wall of the larger blood vessels. This picture is the same in both procedures, the dilatation of the capillaries becoming more conspicuous after several months.

On the side of ligation we find in the first week an extreme stasis in the pulmonary circulation affecting also the nutritive bronchial arterial system. The capillary walls become permeable. In the first days a serous transudate fills out some of the alveoli. This is followed in some areas by an emigration of red and white blood corpuscles into the alveoli. In other places desquamated alveolar epithelial cells mixed with red corpuscles are seen in the alveolar cavities. When the alveoli are not filled with blood corpuscles the dilated capillaries fill out a part of the alveoli. After ligation alone this stasis is not so marked as when the diaphragm is paralyzed; then we find a greater stasis in the lower lobe, adjacent to the diaphragm. At the end of the first week the general stasis is the most marked, causing in some areas a picture very similar to a hemorrhagic infarct, the alveoli being filled with well-preserved or partly disintegrated red blood corpuscles. In some places the nuclear stain of the alveolar epithelium is poor. Close by we find a region where the alveoli are partly replaced by hugely dilated capillaries; or they are free but contain desquamated epithelial cells. After two weeks, the picture changes, the bronchial circulation having become effective. The

alveoli are free, some containing faded red blood corpuscles and alveolar epithelial cells filled with granular blood pigment. The dilatation of the pulmonary arterioles, and in some places also of the capillaries, is very conspicuous. The alveolar epithelium is in rapid proliferation. Nowhere do we find scarring pointing to the organization of a true hemorrhagic infarct. In the absence of any complicating factors, such as heart weakness or infection, the lung is able to overcome this temporary state of undernutrition, lasting for about a week.

At three weeks, a proliferation of spindle cells along the blood vessels, and also within the alveolar septa around the capillaries, sets in, appearing earlier in those cases with phrenicotomy. At 3 to 4 weeks, they form in this series strands of cellular connective tissue dividing the uniform arrangement of the alveoli into lobules. The dilatation of the arterioles and capillaries is still conspicuous. These spindle cells dominate within the alveolar septa, the rather cubical epithelial cells becoming less numerous. Within these strands phagocytic epithelial cells and macrophages with pigment can be seen; some are still lying in the lumina of the alveoli. The lower lobe is more advanced in this early stage of fibrosis than the upper one, giving a further illustration of the effect of the immobilization of the diaphragm.

After ligation alone the proliferation of these spindle cells arising from the adventitial connective tissue of the blood vessels is much slower. Even after two months we find no trabeculation. The alveolar cells are quite numerous. Gradually the spindle cells become more conspicuous, until they finally dominate the picture.

At four and four and a half months the difference between the two series is striking. In cases with ligation alone proliferation of the adventitial tissue along the capillaries within the alveolar septa makes them considerably more prominent. Epithelial cells are relatively rare. Along the larger pulmonary vessels and the bronchi this increase of cellular connective tissue is visible. No trabeculation dividing the areas of alveoli into lobules can be detected. The capillaries still show a marked dilatation (fig. 8.).

When the diaphragm is paralyzed at the time of ligation, the strands of young fibrous tissue are discernible, giving to the section a characteristic appearance of trabeculation. Within these strands the alveoli show a proliferation of their adventitial cells and dilatation of the capillaries, thus preparing for a further division of these small lobules into smaller ones by further strand-formation. In the lobe adjacent to the paralyzed

diaphragm this process is the most advanced, the upper lobe being more in the intermediate stage. At this stage only a few alveolar epithelial cells are seen (fig. 9). Hand in hand with this increase of fibrous tissue goes an increase of elastic fibres (fig. 10).

After three months a thickening of the thin elastic fibres around the smaller blood vessels and an increase in their number are recognizable. At first this process is equally advanced in both series, but later the picture changes. Within the strands of young connective tissue we see these elastic fibres running in a parallel direction. They branch off into enlarged alveolar septa and communicate with fibres in these walls. In this way they give a clue to the formation of these strands. They arise from the crowding together of thickened alveolar walls, with obliteration of the intervening alveolar spaces. On the nonligated side no increase of the elastic fibres is noticeable. Rather they are put on the stretch by the dilatation of the alveolar septa, so that Kawamura speaks of a reduction of the elastic fibres.

Compared with Kawamura's findings, our fibrosis after ligation seems to be retarded; he gives an illustration after one month in which no characteristic feature of lung tissue is visible. A uniform young connective tissue is found all through the section, as if we were dealing with an organized hemorrhagic infarct. The extensive thickening of the pulmonary pleura is a striking difference between our findings and the results obtained by Bruns, Sauerbruch, and Kawamura. As explained above, there is no reason why the pleura should be particularly thickened, except in the presence of some complicating factors, such as oozing or mechanical traumatism at the time of operation. These extensive adhesions, with complete obliteration of the pleural cavity, explain very well the thoracic deformity described by these authors and missing in our series.

In summing up our experiments we find that, in ligation of the pulmonary artery combined with phrenic nerve resection, we have a method which puts the lung at complete physiological rest by direct action. Our experiments show clearly the anatomic changes which take place within the first four months. They are found to be in entire harmony with the underlying physiological changes. In a subsequent longer-standing series we will follow the anatomic changes with regard to the time necessary to get a dense fibrosis, which, under pathological conditions, would be superimposed on the fibrous envelope of reaction and

isolate any localized chronic inflammatory focus in a lung, especially with regard to chronic advanced forms of unilateral tuberculosis.

4. CLINICAL EXPERIENCES WITH LIGATION OF THE PULMONARY ARTERY

Ligation of the pulmonary artery has been used by a few surgeons in some cases with good results. The procedure was never standardized for certain definite conditions, since clinical experience was too small. With the development of extrapleural thoracoplasty the method was unfortunately dropped.

Ligation combined with resection (*Exairesis*, Felix) of the phrenic nerve has never been used. Goetze and Frisch reported good results from the latter procedure in cases of unilateral tuberculosis in which the lesion was restricted to an area adjacent to the diaphragm.

A brief review of our small clinical experience may be added to our experimental findings, by way of demonstrating that the results obtained with each one of the two procedures encourage us to enlarge our clinical knowledge, particularly by combining ligation of the pulmonary artery with phrenic nerve resection as a more promising procedure.

Sauerbruch (1911) reported two cases of unilateral bronchiectasis in which the condition was markedly improved following ligation. In both an extensive shrinking of the organ took place, reducing the expectoration by collapse of the cavities. In both, also, Sauerbruch emphasizes the fact that ligation was performed without any immediate or late subjective or objective discomfort arising from the procedure itself. Willy Meyer (1912) published three cases of bronchiectasis treated in the same manner. Two were benefited; one remained unimproved. None of these cases were cured. All the cases were combined with thoracoplasty, to meet the great retraction of this side of the chest.

Through the courtesy of Dr. v. Voornveld (Zürich-Davos) I am reporting two additional cases operated on by Prof. Wilms (Heidelberg), which were clinically cured by this procedure without any thoracic deformity, and thus making a preliminary or subsequent thoracoplasty unnecessary.

Case 1: Miss M. K., Odessa, was in Davos in August, 1912, for bronchiectasis of the right lower lobe. For two years she had remittent fever. No tubercle bacilli were found in the sputum. The Wassermann reaction was negative. On September 12 Prof. Wilms ligated the lower branch of the right pulmonary artery. The patient had no immediate or late discomfort

from the procedure itself. She made an uneventful recovery. In December, 1912, she was afebrile and practically without expectoration. In July, 1914, Dr. v. Voornveld got word that the patient felt perfectly well and was without any elevation of temperature and without expectoration.

Case 2: P. J. S., engineer, India, 35 years old. In May, 1910, he was the victim of an automobile accident. No objective findings of any injury could be made out, but since that time the patient had had fever, accompanied by an unproductive cough. His condition was growing worse. In November, 1910, he had an hemoptysis. He came to Davos seeking medical advice.

In May, 1911, Dr. v. Voornveld found him an emaciated patient with infiltration of the right upper lobe. A dull area over the right lung was explained as the residuum of an exudative pleurisy. The sputum contained tubercle bacilli. Temperature about 38°C. In Davos the tuberculous process was gradually abating. A bronchitis, however, persisted. A change of climate was considered. In June, 1911, the patient went to San Remo (Italy). In March, 1912, Dr. v. Voornveld was called to San Remo in consultation. The patient's condition was getting worse. He had a persistent high fever. On the right side a large exudate was present, and the patient had copious expectoration containing tubercle bacilli. Dr. v. Voornveld thought of a tropical liver abscess rupturing into the right lung at the time of the automobile accident, that this had activated a tuberculous process present for years in the right upper lobe and that the tuberculous process becoming quiescent during his stay in Davos was now active again. Dr. v. Voornveld's suggestion was to ligate the right pulmonary artery in one stage and to open the abscess at a second operation.

On June 5, 1912, Prof. Wilms withdrew, by thoracocentesis, 700 cc. of serous fluid from the right chest. The patient felt much better. On June 14, Wilms ligated the right pulmonary artery through a posterior approach. Involuntarily, he opened at the same time a huge abscess of the lower lobe. The patient made an uneventful recovery. Three weeks after the operation he was out of bed. The temperature was slightly elevated in the evening (37.5°C.). He coughed three to four times a day. The abscess cavity drained for one month, then subsided within a short time and closed by granulation. The patient returned to India and regained perfect health. He is still active as an engineer and is as healthy as ever.

These two clinical observations show that ligation gives complete clinical cure within a relatively short time and does not necessitate any thoracoplasty, especially when compared to the palliative procedures hitherto used for these serious conditions. In cases of chronic tuberculosis

without complicating factors, such as abscess or bronchiectasis, ligation has never been used. Extrapleural thoracoplasty has been found so satisfactory that no improvement of the technique by another procedure has been thought of. In the two cases reported no thoracic deformity resulted as a late effect. This proves that ligation alone, without the chest deformity resulting from thoracoplastic procedures, is sufficient to secure permanent cure in these lung conditions.

Observations made upon cases of one-sided congenital or acquired atelectasis have proved the movability of the mediastinum in such conditions. Rohmer and Borchardt published a case of atelectasis of the left lung in a young woman without any thoracic deformity. No heart symptoms were present. She died of meningitis following otitis media. At necropsy the heart was found pushed away over to the left and occupying a space between the left posterior axillary line and the left sternal border. A huge enlargement of the right lung was noticed, the right upper lobe filling the cupola of the left side completely. Also, the middle lobe extended over to the left. No dilatation of the heart could be made out. The left lung formed a shrunken sac filled with sebaceous-like material. The cause was a complete obliteration of the main bronchus by scar tissue, probably syphilitic in origin. Schuchart describes a case in which the thorax showed a normal appearance also. At autopsy the atelectatic left lung was the size of a fist. The hypertrophic right side extended to the left mammillary line, the left cupola being occupied by the right upper lobe. The left lung was a shrunken mass, lying posteriorly next to the spine. The heart was pushed far backward and to the left, with dilatation of the right ventricle. v. Recklinghausen refers to a case of atelectasis of one lung without any deformity of the thorax, although a great displacement of the mediastinum and of the heart had taken place. Coats mentions a man of 46 years with atelectasis of the left lung with a finding analogous to the observations just mentioned.

These clinical facts point to the great importance of the mediastinum, also in man, as a movable structure, which will give way to a great extent if one lung has to expand, thus compensating the other side put at complete physiological rest by ligation. We are not forced to mobilize the chest wall and thus change the whole static condition of the trunk, with secondary arthritic changes in the spine causing, in the course of time, perhaps new symptoms of discomfort for the patient. The paralysis of the diaphragm by phrenicotomy, the subsidiary procedure

in our proposed operation, was used hitherto as a diagnostic measure, to test the functional efficiency of one lung for the whole respiratory function (Stuertz, Sauerbruch, Schepelmann). Goetze and Frisch reported recently good results by this form of immobilization of one lung in chronic tuberculosis restricted to the lower lobe.

CONCLUSIONS

This clinical survey, together with our experimental findings, points to ligation of the pulmonary artery combined with resection of the phrenic nerve, as a method which promises an enlargement of the indications for a rational surgical procedure in advanced unilateral tuberculosis, in cases either benefited by methods now used after a great length of time or not improved at all, and so facing a dark prospect.

Other chronic inflammatory conditions of the lung, such as abscess, bronchiectasis, anthrax and even new growths in their early stages, might be treated with a much brighter prospect of cure than hitherto. In an early stage the diseased organ might be put at complete rest by ligation of the pulmonary artery combined with resection of the phrenic nerve. The intact side takes over the whole respiratory function. A fibrosis occurs on the ligated side around the diseased area, in addition to the natural fibrous envelope present in all these conditions. Thus well prepared, the diseased organ might be extirpated in a subsequent operation with a much brighter outlook than when undertaken in a one-stage operation.

This branch of surgery and its further development demands the intimate coöperation of surgeon and physician; together they must make repeated and thorough examinations of the case. Only after continuous observation and deliberation can the indications for a surgical procedure be considered and then operation should be done only by a man of experience along this special line.

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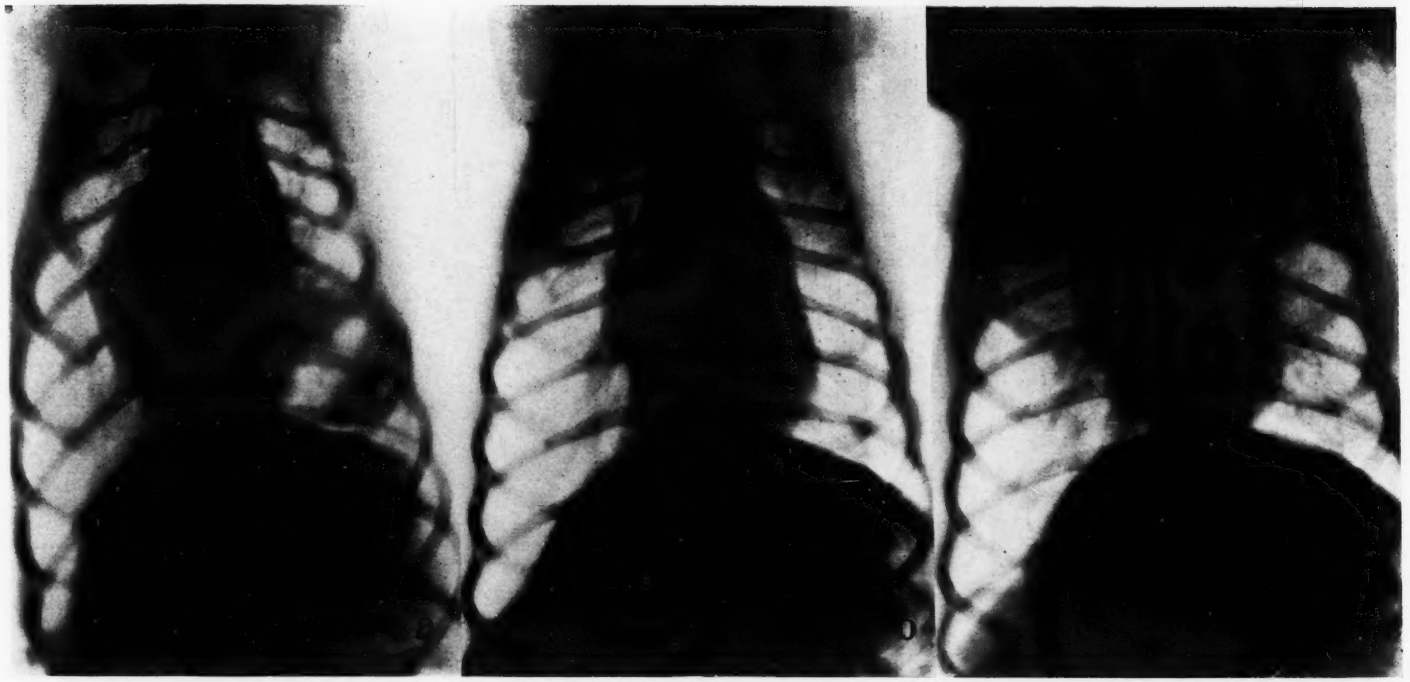

FIG. 1a, 1b, 1c. X-RAYS OF THE CHEST (DOG) FOLLOWING LIGATION OF THE LEFT PULMONARY ARTERY COMBINED WITH RESECTION OF THE PHRENIC NERVE

1a: 25 days; 1b: 109 days (3½ months); 1c: 166 days (5½ months) after operation. Note the increasing elevation of the paralyzed diaphragm

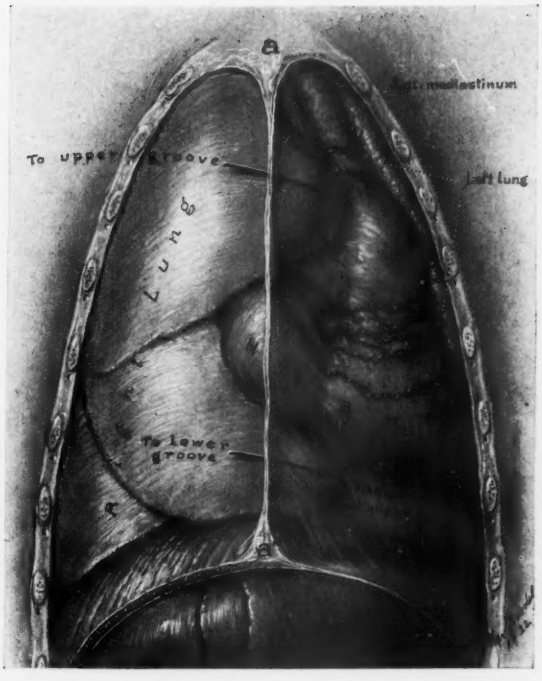

FIG. 2. THE EXPANDING INTACT RIGHT LUNG PUSHES THE ANTERIOR MEDIASTINUM TO THE SIDE OF LIGATION, THUS FORMING HOLLOWS IN THE PHYSIOLOGICALLY WEAK PLACES OF THE MEDIASTINUM (UPPER AND LOWER GROOVE)

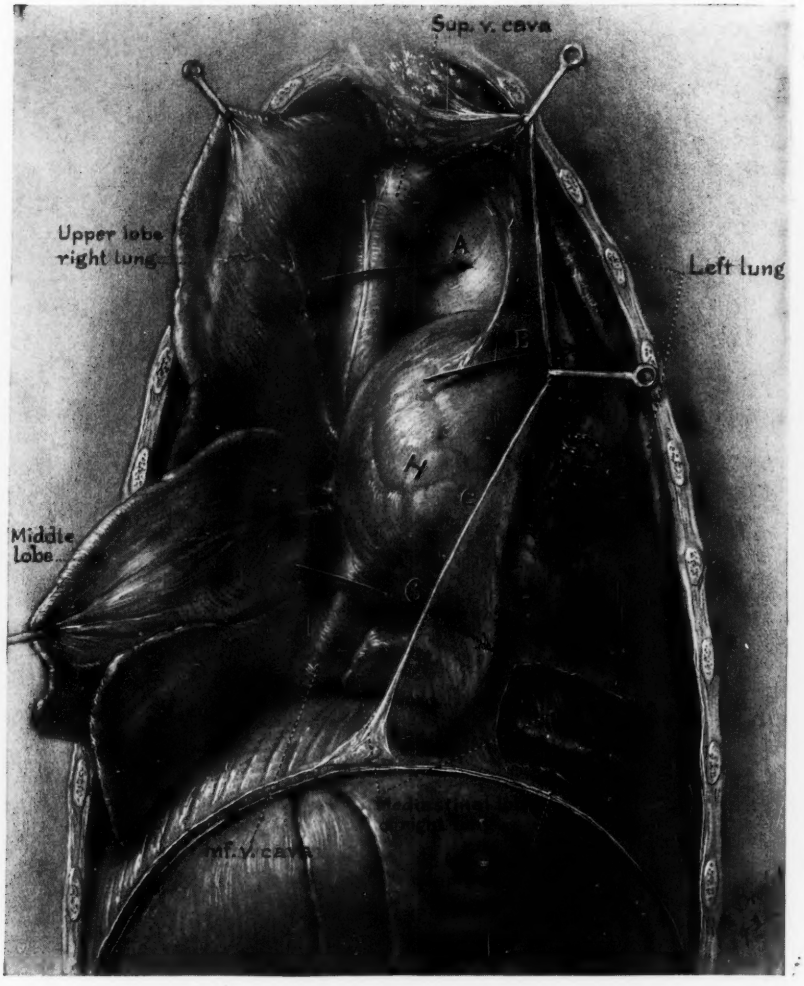

FIG. 3. SAME AS FIG. 2

The right mediastinal lobe expands behind the inferior vena cava to the left lateral chest wall. (Figs 2 and 3 are drawings made from a specimen in which a partial occlusion of the pulmonary veins on the left side was performed. The displacement of the mediastinum is the same as observed after ligation of the pulmonary artery.)

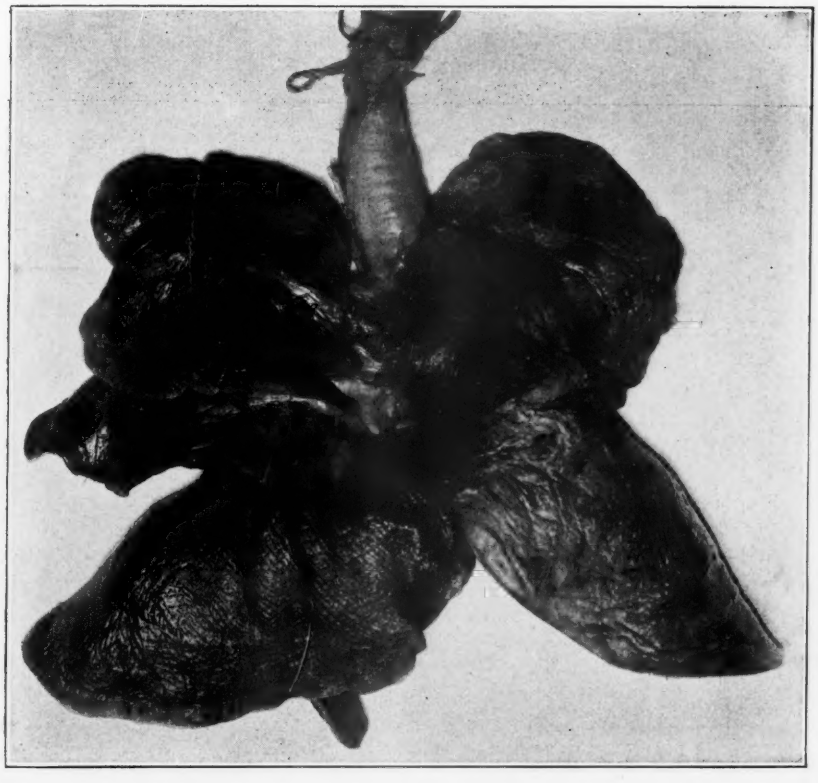

FIG. 4A

FIG. 4a. and 4b. PHOTOGRAPHS OF LUNG SPECIMENS 2 MONTHS (4a) AND 4 MONTHS (4b) AFTER LIGATION OF THE LEFT PULMONARY ARTERY

Relatively small difference in size betwen right and left lung

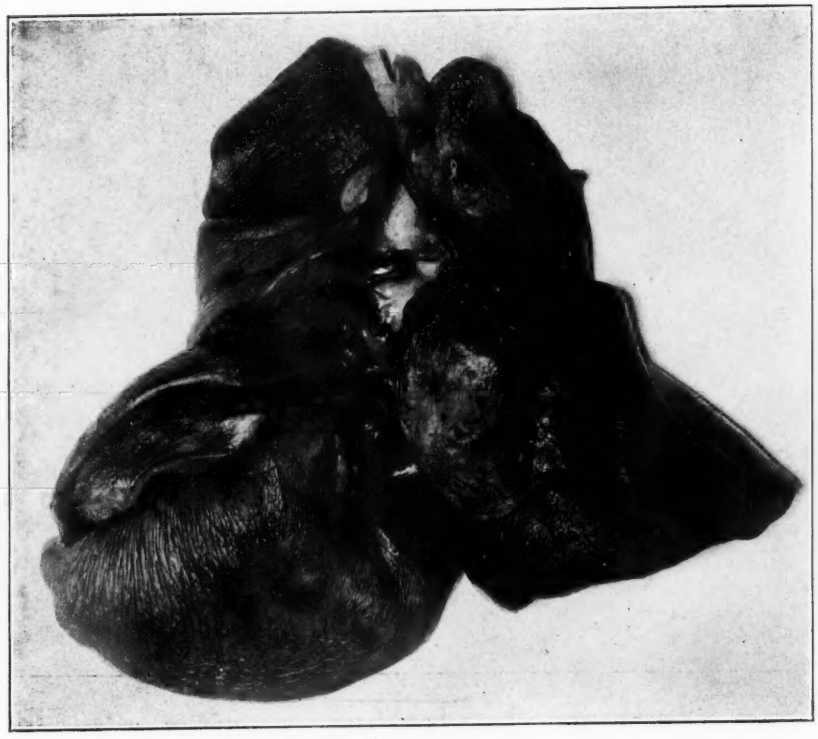

FIG. 4B

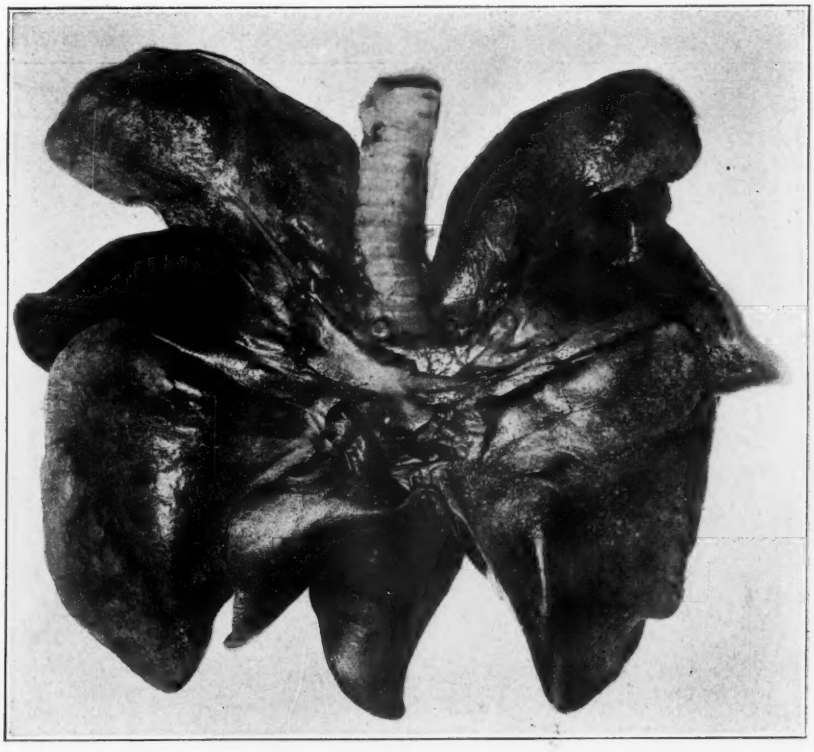

FIG. 5A

FIG. 5a, 5b, 5c. PHOTOGRAPHS OF LUNGS 1 DAY (5a), 24 DAYS (5b), AND 136 DAYS (5c) AFTER LIGATION OF THE LEFT PULMONARY ARTERY COMBINED WITH RESECTION OF THE PHRENIC NERVE

Note the marked gradually increasing contraction of the side of ligation

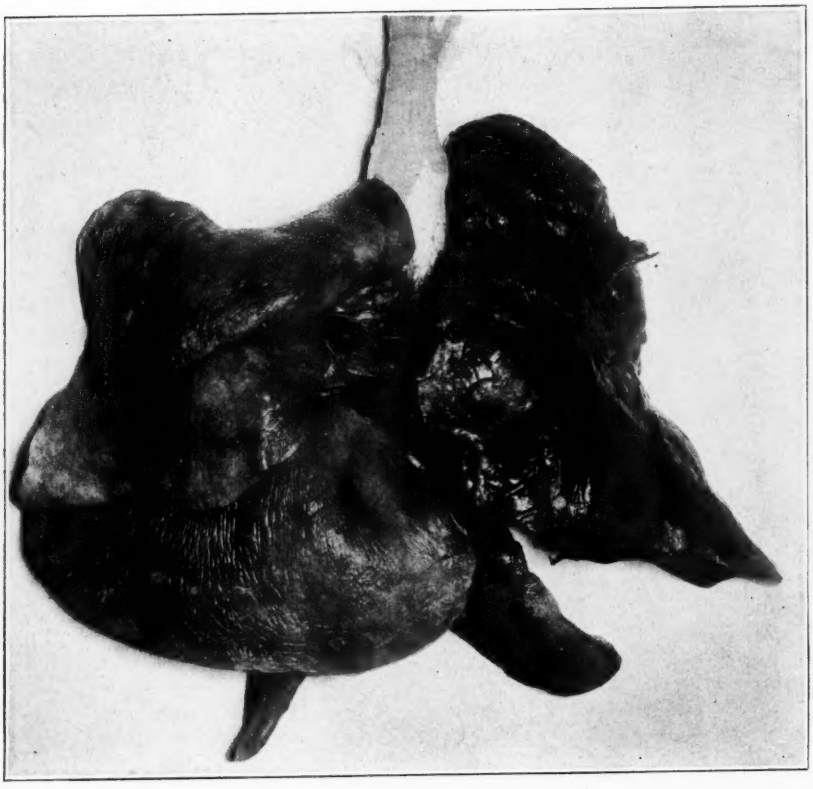

FIG. 5B

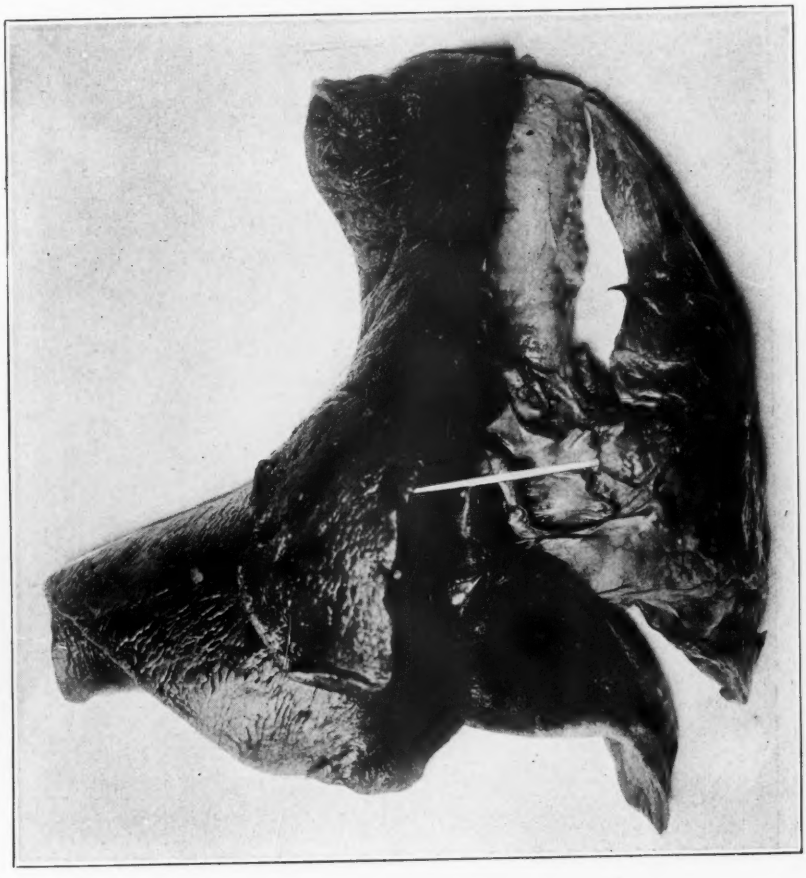

FIG. 5C

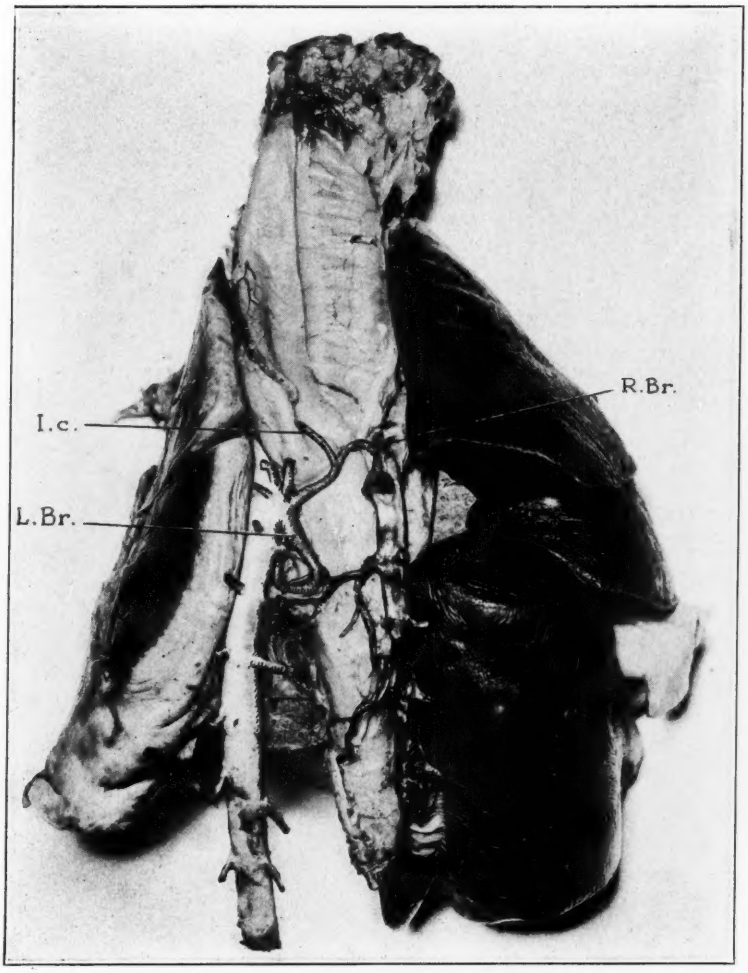

FIG. 6. PHOTOGRAPH OF A LUNG 140 DAYS AFTER LIGATION OF THE LEFT PULMONARY ARTERY COMBINED WITH CRUSHING OF THE PHRENIC NERVE (VIEW FROM BEHIND)

Note the difference in size of the right and left lung. The *left* bronchial artery (L.Br.) is more than double the calibre of the right one (R.Br.), giving off an intercostal branch (I.-c.)

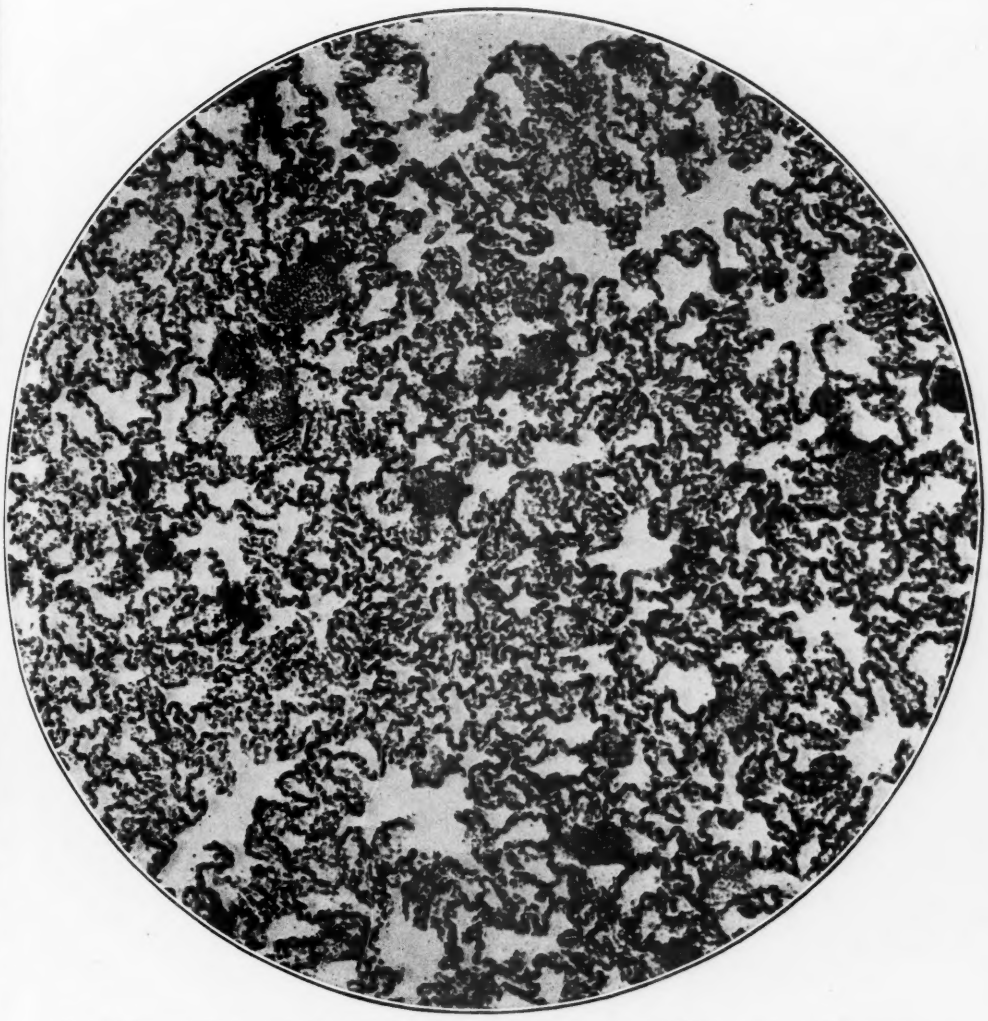

FIG. 7. PHOTOMICROGRAPH THROUGH THE INTACT RIGHT LUNG 136 DAYS AFTER LIGATION OF THE LEFT PULMONARY ARTERY COMBINED WITH RESECTION OF THE PHRENIC NERVE

Note the great dilatation and tortuosity of all the smaller blood vessels and capillaries. No connective-tissue proliferation in the perivascular or peribronchial tissue.

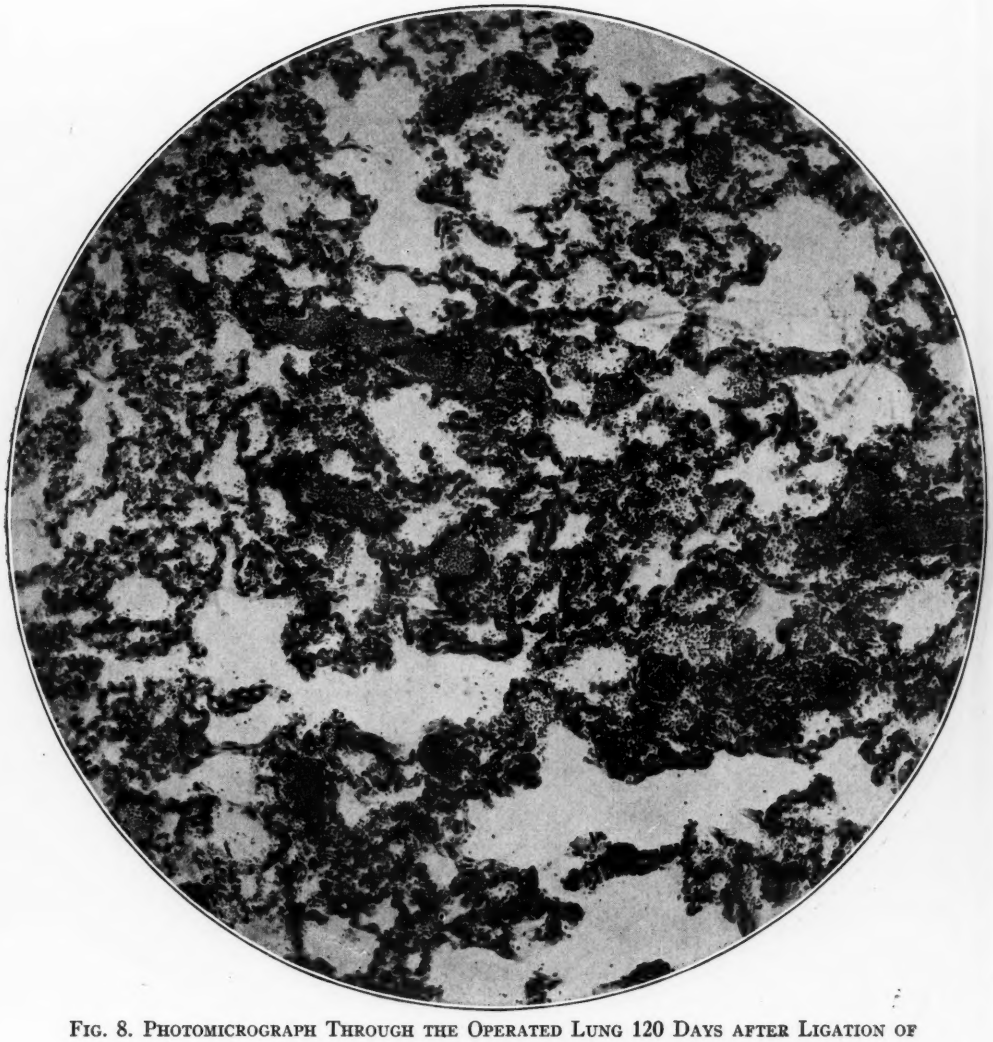

FIG. 8. PHOTOMICROGRAPH THROUGH THE OPERATED LUNG 120 DAYS AFTER LIGATION OF THE PULMONARY ARTERY

Dilatation of all the smaller blood vessels and capillaries. Connective-tissue proliferation within the alveolar septa and the peribronchial and perivascular tissue. No trabeculation visible.

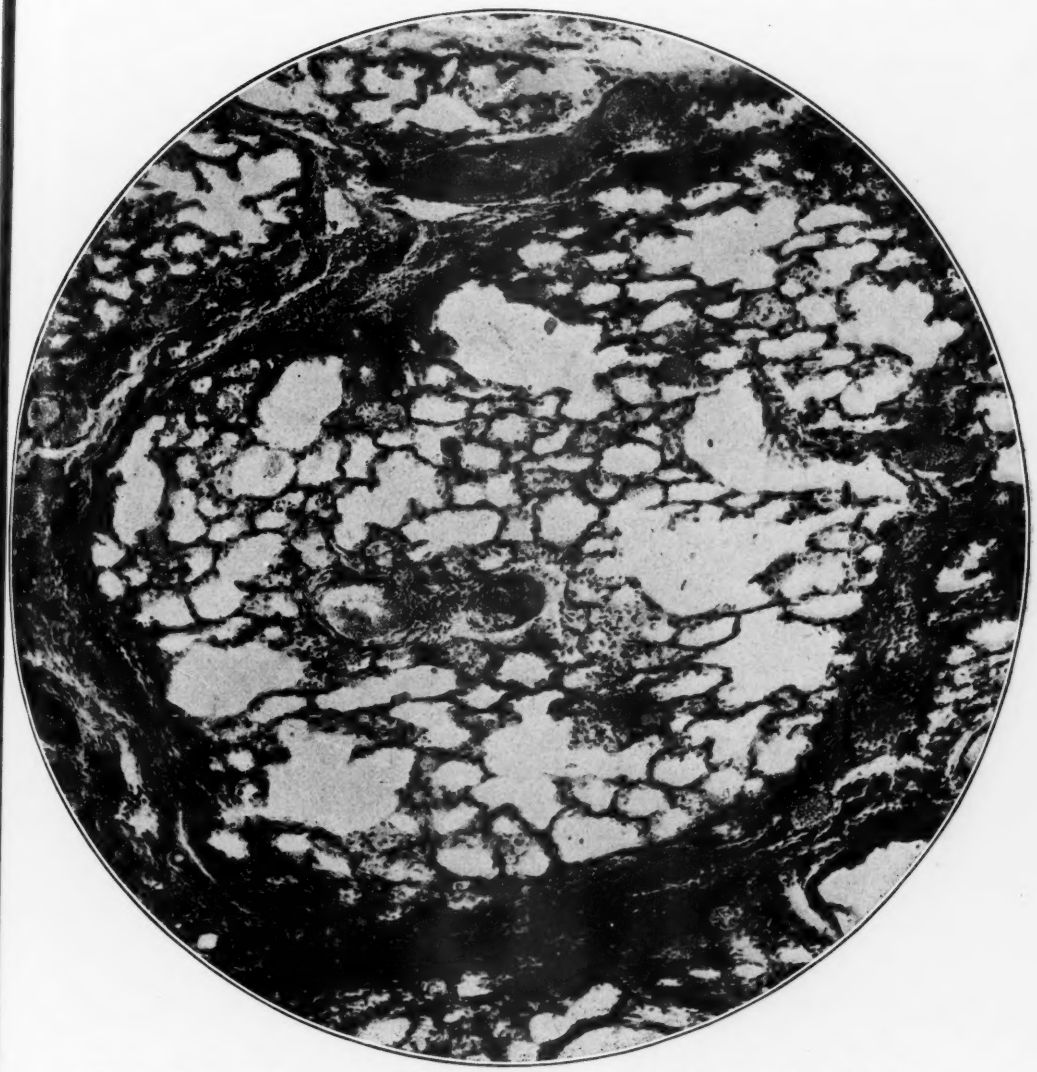

FIG. 9. PHOTOMICROGRAPH OF THE LEFT LUNG 136 DAYS AFTER LIGATION OF THE PULMONARY ARTERY COMBINED WITH RESECTION OF THE PHRENIC NERVE

Connective-tissue proliferation in the perivascular and peribronchial areas gives rise to the formation of strands which cross the field in various directions. Thickened alveolar septa bring about the collapse of the alveolar spaces.

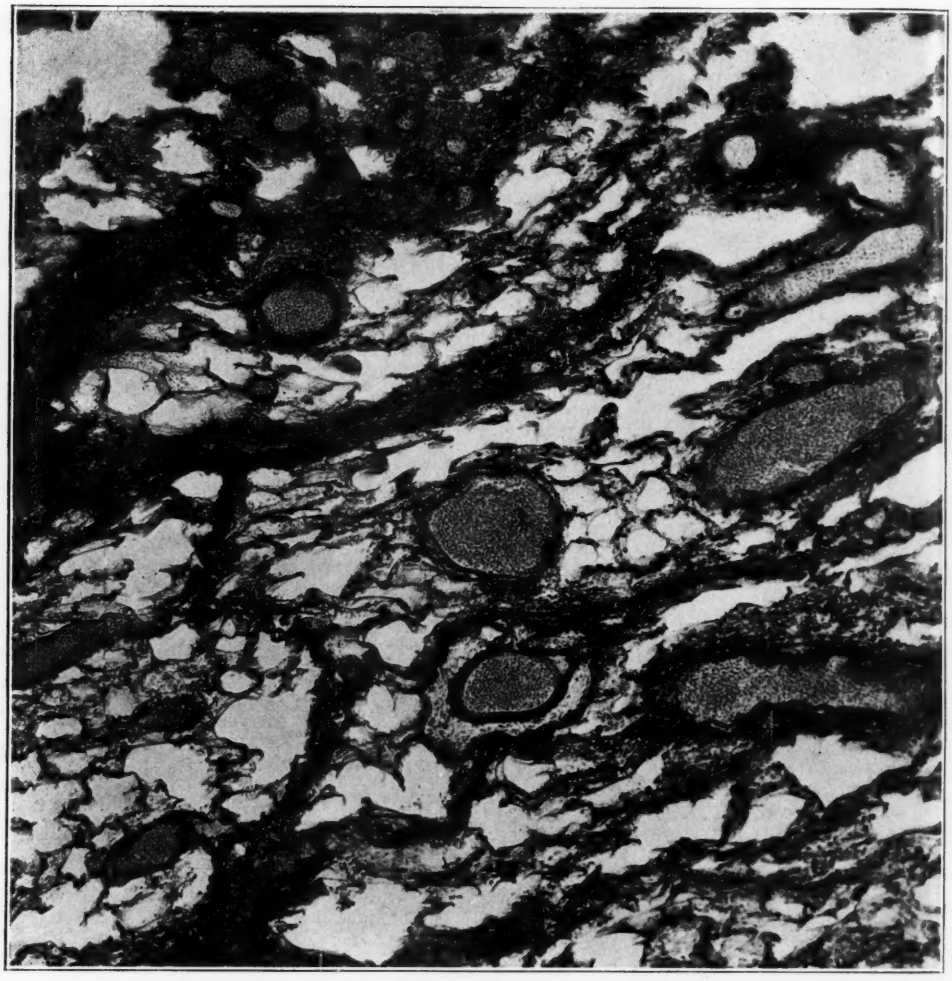

FIG. 10. PHOTOMICROGRAPH OF THE SAME SPECIMEN AS FIG. 9. WEIGERT STAIN

Increase of the elastic fibres within the new connective tissue (strands). Branching into the thickened alveolar septa conspicuous.

THE THORACOSCOPE IN PULMONARY DIAGNOSIS[1,2]

J. J. SINGER

It is with an apology that I am presenting this short paper before the National Tuberculosis Association. The subject is brought up as much to obtain information as to give anything especially new on the subject. I am in hopes that the presentation of a few observations while using thoracoscopy might be of some interest. Since the publication of the papers on thoracoscopy by Jacobaeus (1), Korbush (2), and Unverricht (3), I have attempted to use the method with more or less modification.

For some reason medical men, as distinguished from surgeons, are very prone to make every effort to prevent operation and most of us doing chest work will go a long way to escape the surgeon's knife. In spite of being associated with Doctor Graham in surgery of the lung, I have not yet overcome that feeling of fear. When one considers that in the use of thoracoscopy we have a means by which the pleural cavity can be explored through a relatively small instrument without rib resection, and when one considers that certain operations can be made through this instrument, it is reasonable to expect medical men to make use of this method. On the other hand, we have learned through the wonderful work of Doctor Graham and Doctor Bell (4) that it is possible to open many chests with impunity, provided the openings are not too large. They have shown, also, that it is possible to open both sides of the chest at the same time without doing serious damage to the patient's condition. Whether to use the first method, that is thoracoscopy with the thoracoscope, or closed method, or to fearlessly open the pleura and inspect the cavity, is the problem that I am bringing before this Association.

Kelling in 1902 (quoted by Unverricht) first used an endoscope and trocar in experimental work on chests in animals. Jacobaeus used simi-

[1] From the Department of Internal Medicine, Washington University School of Medicine, St. Louis.

[2] Read before the clinical section at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 7, 1924.

lar methods in 1912 and then used human subjects. He reports 50 cases in which he used thoracoscopy and cauterization of adhesions in pulmonary tuberculosis. He also devised an instrument for this purpose. Unverricht used this method, but modified the instrument of Jacobaeus which he claims gave a clearer vision. He observed, however, that in removing adhesions by cautery large blood vessels and sections of the lung may be severed, and he shows by microscopic sections how it is possible for adhesions to have lung tissue herniate into them. He explained why hemorrhage occasionally results from Jacobaeus's operation. Originally the thoracoscope was used for inspection only, and Jacobaeus is entitled to the credit of showing the possibility of severing adhesions through the instrument to produce better collapse in pneumothorax. These three authors have used local anesthesia, forcing the thoracoscope through the pleura and then aspirating any fluid that is present. When adhesions are found, another trocar is inserted near the adhesions and a galvanocautery is inserted through the trocar. With these two instruments in the chest cavity the cautery is directed by use of the thoracoscope against the adhesions and the current is turned on.

I have not had the privilege of seeing anyone use thoracoscopy, nor do I know of any work along this line done in this country; at least there is no mention in the American literature of any similar work having been done in America. The method seems to offer many possibilities to men doing chest work. I, therefore, designed an instrument patterned somewhat on Jacobaeus's thoracoscope.[3] I have an attachment for the side opening through which various bronchoscopic instruments can be introduced under direct vision for removal of sections, and also one through which one can drain fluids and replace these with air. There is a small light in the tip of the instrument, so that vision can be had with or without the cystoscopic atttachment. The photographs are self-explanatory. It is also possible to do operative work through one opening in the chest cavity. This, I believe, is a distinct advantage. But, when one attempts to do thoracoscopy through the small openings, it is not as easy as one would infer from the descriptions seen in the literature.

The method that we use is as follows: A pneumothorax is produced in the involved side by the ordinary method. With the patient placed

[3] William A. Phillips, Surgical Electrical Instruments, St. Louis.

under more or less deep twilight sleep the skin is anesthetized with 0.5 per cent novocain and an incision is made in the intercostal space with an iris knife. Through this incision the instrument is introduced into the pleural cavity. I might note here that it is very difficult in a large number of cases to find intercostal spaces wide enough to introduce the instrument without scraping the periosteum of the ribs. This, of course, causes considerable pain and occasionally hemorrhage from laceration of the intercostal artery. With the instrument in the chest, the trocar is removed, closing the valve as it nears the end of the instrument; and a baby cystoscope is then introduced, opening the valve to admit it. The purpose of the valve is to keep the chest cavity unexposed to the outside air during the entire operation. It is possible now to inspect the chest cavity; the character of the fluid can be noted, small nodules and patches of calcification on the pleura, tumor masses, areas of congestion and even small abscesses of the lung can be seen. However, if the patient is only anesthetized locally, there is some pain when the thoracoscope is pointed up toward the apex. If adhesions are encountered, it is possible through the side opening to introduce a high-frequency electrode to sever adhesions. When the cystoscopic instrument is removed and an ordinary eyepiece is used, one is able to pick out small areas of pathological changes that need attention. Experimentally, on animals with flexible ribs, one can make a clean sweep of the pleural cavity with little difficulty. One is able to see as much in the chest cavity with the instrument as is possible in the bladder with an ordinary cystoscope. It takes considerable experience, however, to interpret the various images and relative positions of conditions noted in the chest.

The advantages of this method are (1) only a small incision is necessary in the chest wall, (2) there is very slight shock and occasional fever follows the operation, and (3) the patients are not as much disturbed mentally as they would be by a so called operation.

The disadvantages of the method are (1) the image one sees at any one time is small, no matter what system of lenses are used, (2) there is a certain amount of pain in pushing the ribs by moving the instrument to and fro, (3) fluid, so often found in these cases, clouds the lens, which makes it necessary to remove the instrument and reintroduce it, and (4) it takes considerable experience to interpret one's findings.

In the open method of thoracoscopy, that is, opening the pleura under local anesthesia, either removing a portion of the rib or not, one is able to get a direct view of the chest and its contents. If there is any fluid

in the cavity, this is drained, and sections can be removed without any difficulty. Doctor Graham and I have used this method in several cases and have had no serious results follow. It does not disturb the patients any more than thoracoscopy. When one considers how much one can see with this method, its simplicity, and the lack of danger, the two methods are hardly comparable, except in those cases in which it is thought inadvisable to open the pleura.

The question will arise whether it is possible or advisable to open the pleura in tuberculous patients. It is my impression that if so little danger has resulted in opening the pleura in many cases there is no reason why it cannot be done. It is true that tuberculous sinuses occasionally result from the use of needles, and it is possible that tuberculous sinuses might result. Unfortunately, I have not had much experience with this class of cases. It seems that similar good results could be obtained by opening the pleura and exposing the cavity to direct sunlight, as is done in the time-honored operation of opening the peritoneum for tuberculous peritonitis.

Finally, thoracoscopy, in conjunction with physical signs, roentgen-ray plates, the diagnostic pneumothorax of Brauer, and fluoroscopy, makes it possible for the physician interested in chest work to make diagnoses that were formerly impossible.

CONCLUSIONS

1. The use of the thoracoscope is a great aid in the diagnosis of chest conditions.

2. It requires a certain amount of skill to interpret the picture seen through the instrument.

3. Open thoracoscopy, that is, opening the pleura wide, is recommended in more cases as an exploratory operation.

4. More experience with the methods is necessary to make it of general use.

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(3) UNVERRICHT: Ztschr. f. Tuberk., 1922, xxxvi, 267; also J. A. M. A., 1922, lxxix, 597; also Klin. Wchnschr., 1923, ii, 502.
(4) GRAHAM AND BELL: Am. J. M. Sc., 1918, clvi, 839.

PLATE 1. AUTHOR'S MODIFIED THORACOSCOPE

1 represents three sponge holders with protecting plugs, which fit into the side opening at *11*. *2* is a dull trocar which fits into *9* for the introduction of the thoracoscope into sinuses connecting with the pleural cavity. *3* is a sharp-pointed trocar which is used in the thoracoscope in introducing the instrument into the chest cavity where no sinuses exist. *4* is a high frequency electrode, with protecting plug to be noted in the upper part of the wire. *5* is a baby cystoscope, the upper part of which is so modified as to fit into the main shaft of the thoracoscope. *6* represents connecting cords. *7* is a lamp which fits its carrier *8*, and is introduced into the small portion of the tube *9;* the opening at its lowest portion is protected by a small piece of mica, so that at no time can blood cloud the lamp. *8* is the light carrier which is attached and connected with *12* at right angles. *9* is the operating tube which is connected below the valve, and has two cavities, one holding the light carrier, *8*, and the other carries the various instruments to be introduced into the chest. *10* is an ordinary eyepiece with magnifying lens; this lens is removed before the cystoscopic attachment, *5*, is introduced. *11* is the two-way valve, which is attached to the side opening when it is necessary to aspirate fluids, and to replace these with air; this part of the instrument is detached from the side opening when one wants to introduce the electrodes or instruments through the opening in *9*. *12* is the connection for the instrument to cords *6* and is also made heavy enough to form a handle; the large stop-cock is so arranged that instruments can be introduced and removed without allowing the air to run in or out of the chest cavity.

PLATE 1

THE ELECTROCAUTERY IN THE TREATMENT OF LARYNGEAL AND PHARYNGEAL TUBERCULOSIS[1]

JOSEPH B. GREENE

Asheville, North Carolina

The frequency and likewise the seriousness of laryngeal tuberculosis occurring as a complication of pulmonary tuberculosis is my reason for making a plea at this time for a more general use of the electrocautery for the relief of this distressing condition. Various topical applications, sprays and powders have been recommended for the relief of this complication, and their large number in itself suggests that not one of these has proved entirely satisfactory.

St. Clair Thomson, in a recent paper before the American Laryngological Association, said, "I have given up lactic acid, and practically all chemical caustics are found to be ineffective compared to the galvanocautery. It is the one treatment not only for ease but for cure."

It may be of interest also to quote from a recent paper of Levy of Denver, who says

> The galvanocautery is applicable to a very large percentage of cases, either for palliative or curative purposes. In 100 private cases seen in the past few years the writer used it in 22 cases. I am firmly convinced that its use can be extended to nearly every stage of laryngeal tuberculosis after the initial period of anemia or hyperemia—that is to say, in all forms of infiltration, smooth, nodular, papillomatous; in all varieties of ulceration, small, large, sluggish, painless or painful; even in the final stage, when necrosis is involving underlying cartilage, it may relieve suffering and help clean the parts. Applied superficially its value to sluggish ulcerations in removing necrotic tissue and in stimulating granulations is far superior to chemical agents.

A few decades ago Krause and Heryng were strong advocates of the use of the punch-forceps and curette for the removal of both ulceration and infiltration of the larynx, but these radical measures have not

[1] Read before the Clinical Section at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 8, 1924.

found general acceptance by our profession. At the present time, the use of such surgical measures is largely confined to the removal of the epiglottis, and here the use of the electrocautery snare would seem to be a measure of choice. In advocating a more general use of the cautery, it is far from my purpose to claim for it a "cure-all," so to speak, or that it is a measure adapted to every tuberculous larynx. However, in my hands, no other treatment has proved so satisfactory.

In the very early lesions of the larynx, characterized by simple hyperemia, and not causing pain, I am in the habit of depending largely upon vocal rest to secure an arrest, or perhaps a cure of the condition. In speaking of rest to the larynx, I might say that body rest is, at times, just as important for the laryngeal complication as it is for the pulmonary condition. In these early cases graduated solar therapy should prove helpful, though my experience has been too limited to speak with positiveness on the subject. In the late stage of the disease, evidenced by extensive infiltrations and ulcerations of the larynx, particularly if the general condition of the patient is bad, the cautery should be resorted to only for the relief of pain. Here we may meet with disappointment, for, in such cases we may, in the end, be forced to resort to the use of a cocaine spray or the administration of opium in some form.

There are two chief symptoms of laryngeal tuberculosis for which the patient seeks relief: (1) pain and (2) voice disturbance, evidenced by hoarseness or absolute aphonia. Lesions situated in the upper larynx, as in the epiglottis, arytenoids and aryteno-epiglottic folds are essentially painful, while lesions situated within the larynx proper are more commonly associated with voice disturbance, pain being a less disturbing symptom. It can hardly be questioned that the prognosis of the pulmonary lesion is at times largely dependent on our ability to remedy the laryngeal complication, particularly so when pain is a dominant feature and proper nutrition of the patient cannot be maintained. It has seemed to me that the laryngeal complication is often regarded too lightly when the patient is told that the larynx will get better when the general condition improves. This is far from being the case, in my experience. The entire picture changes when we are able to relieve the distressing symptom of dysphagia. Then again, when hoarseness or aphonia is a prominent feature, the mental outlook of the patient is greatly improved when these symptoms are relieved by the action of the cautery. In such cases when fibrosis has

occurred patients can be allowed a return to a moderate use of the voice, provided the larynx is periodically watched with an idea of enjoining silence should the case require such action.

The action of the electrocautery is not to destroy the entire tuberculous area, as is the case in the treatment of malignant growths, but rather to cause a local reaction, bringing fresh blood to the part and producing fibrosis. As Wood says, "The eschar produced by the burning prevents reinfection until the tissue has become sufficiently resistant to protect itself, sealing the lymphatics and blood vessels." This action of the cautery in closing the blood vessels and lymphatics makes it a relatively safe measure for the treatment of infiltrations as well as ulcerations. The fear entertained by some that the action of the cautery might open up an avenue of general dissemination, or be productive of secondary infection at the site of the cautery, has not been borne out by my experience. Swollen and oedematous arytenoids which are often so painful are greatly relieved by igni-puncture. Contrary to one's expectations, the reaction is not great, and the reduction of swelling may avert an impending tracheotomy. This, I feel sure, was the case in my early experience with the cautery.

Ulcerations occurring so often on the dorsal side of the epiglottis respond readily to the action of searing with the cautery. Oedematous epiglottides are greatly benefited by a few punctures of the cautery point. Lesions of the epiglottis have usually been considered as having a bad prognosis, not only on account of the severe dysphagia interfering with the taking of food, but also as being very resistant to the usual methods of treatment.

Tuberculous infiltrations or ulcerations when localized on the vocal cords or ventricular bands respond well when lightly touched with the cautery point. However, in such lesions great accuracy of technique is required, and caution should be taken not to burn too deeply on account of the delicate musculature of the larynx. Tuberculous infiltrations and granulations, occurring in the posterior commissure, which are so frequently associated with hoarseness or aphonia, respond well to the action of the cautery.

There are two methods of applying the cautery, the direct and indirect. In my experience, the operation can be very satisfactorily done by the indirect method with the use of the laryngeal mirror, which makes it an office or even a bedside procedure. The direct method usually requires suspension of the patient on a table, a special equip-

ment not always available. The fact that such careful workers as Dean and Arrowsmith advise the direct method of application by suspension convinces me that it possesses distinct merit.

We should bear in mind that the laryngeal lesion is only a complication of pulmonary tuberculosis, though it often seems the sole lesion or, at least, the most important one to the patient. Any method, however, is doomed to failure which does not take into consideration such general hygienic measures as rest, proper food, fresh air and a suitable climate.

It has seemed to me that there is danger of too much dependence being placed on silence, or so called vocal rest, in the treatment of laryngeal tuberculosis. So long as the patient has a cough and must perform the functions of swallowing, absolute rest to the larynx cannot be attained. It is manifest that in the larynx absolute fixation cannot be secured as in joint tuberculosis by the use of splints or plaster casts. Then again we have in the larynx, unlike in the joints, a region relatively accessible for appropriate local treatment. As desirable as vocal rest is in the early stages of the disease, and whenever there is evidence of activity, I have never felt sure that, in the chronic type showing evidence of fibrosis, moderate talking, short of fatigue, was harmful to the larynx. When the epiglottis is the site of the lesion, we know that complete silence does not in the slightest degree affect the course of the disease.

Before concluding this paper I should like to speak briefly of pharyngeal tuberculosis, a condition, though less common than laryngeal tuberculosis, that is important on account of its unfavorable prognosis. There are two very distinct types of this complication, differing both in appearance and in clinical course. In one there is noted a grayish color of the mucous membrane of the pharynx, associated with some oedema of the submucous tissue, with here and there small tubercles projecting slightly above the surface. These areas finally break down with the characteristic appearance of a superficial ulceration. Pain at this stage becomes marked, particularly if the pillars are involved. This lesion of the pharynx seems to be a miliary infection, and has proved as hopeless here as when encountered elsewhere in the body. In one case in which the pain seemed unbearable, I was tempted the use of the cautery without influencing favorably either the pain or the progress of the disease. The other type of pharyngeal tuberculosis is characterized by indolent-looking ulcers often surrounded by raised

infiltrated edges. These lesions are often situated on the posterior pharyngeal wall, though at times they encroach on the faucial pillars. As a rule, the pain is not great, but if the lesion is not averted it will spread until the entire pharyngeal wall is involved in the ulcerative process. This type of lesion responds most happily to the action of the electrocautery and a cure can be predicted with full confidence.

In conclusion, I would say that if I have succeeded in arousing your interest in a method of treatment which promises so much relief for your patient and satisfaction to yourself, I shall feel justified in taking your time for the presentation of this subject.

STUDIES ON THE WILDBOLZ AUTO-URINE REACTION[1,2]

JOHN J. ENRIGHT AND LEO F. RETTGER

The great prevalence of tuberculosis and the difficulty of diagnosis, especially in the early stages, have been responsible for a vast amount of literature on laboratory tests designed to aid in diagnosis. Reports of studies on tuberculin tests, agglutination, precipitin, opsonic-index, and complement-fixation reactions have already reached almost unlimited proportions. Various modifications of tuberculin tests have been introduced, held sway for a time, and then for different reasons been discarded until now the intracutaneous method of injection is probably the most commonly practised. Although this modification of the original tuberculin skin test is thought by some workers to be of value in diagnosis of clinical disease by the great majority, and probably rightly so, it is looked upon as an aid merely in detecting little more than tuberculous infection and not necessarily an active diseased condition.

The agglutination, precipitin and opsonic-index reactions have never gained much prestige as an aid in the diagnosis of tuberculosis, but the complement-fixation test is still making a strong bid for practical use. The innumerable studies that have been reported on this latter phase of tuberculosis research offer such differences of opinion that they are bewildering. The great number of basic experimental factors, which may play such an important part in the rather complicated technique of complement fixation, will probably hinder for some time the attainment of confirmatory results in the different laboratories.

The important part that accurate diagnosis, especially in the early stages, plays in overcoming the disease makes it desirable that any new diagnostic help promised in this field be given serious consideration. In 1919 Wildbolz introduced such a test and claimed that he could tell whether a person harbors active tuberculosis by determining the presence or absence of tuberculous antigen in the patient's own urine. He used

[1] From the Department of Bacteriology, Yale University, and from the U. S. Veterans' Hospital no. 41, New Haven, Connecticut. Submitted to Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, May 1, 1923.

[2] Approved for publication by the Director of the United States Veterans' Bureau.

the intracutaneous skin test on allergic individuals with the patient's urine concentrated to one-tenth of the original volume. Wildbolz placed great value on the reaction, and his opinion in this respect has already been confirmed by a number of workers. However, there is perhaps an almost equal number of investigators who take issue with Wildbolz, many of them going so far as to deny any value whatsoever in the test.

At least forty papers have been reported on the clinical application of the test. Closer agreements than those that have appeared should be arrived at by more fundamental studies on the nature of the urinary antigens and methods of purification. Lanz (1920) and Von Bergen (1921) have already made advances in this direction. It is the purpose of this paper to emphasize these phases of the problem, after first repeating some of Wildbolz's work, using his technique without any modification.

Most of the papers on the auto-urine reaction have come from the hands of German authors, a relatively few from the French, and still fewer from Italian, Swedish, English, and American workers. To the writers' knowledge only two papers have appeared in this country, those of Gibson and Carroll (1921) (1922).[3]

I. HISTORICAL REVIEW

Although Wildbolz was the first to use the intracutaneous skin test to demonstrate tuberculous antigen in urines, there had been many previous attempts to search for antigen by other means. Maragliano (1900) was the first worker to test for tuberculous antigen or toxin in blood and urine. He injected the whole blood, the serum, and glycerine extract of blood and urine into mice and guinea pigs. He found that these animals died or lost weight more quickly than the controls. Lüdke (1907) doubted Maragliano's findings, inasmuch as all of his own results were negative.

Marmorek (1909), using complement fixation, reported favorable results in his tests for tuberculous antigen in blood serum and urine. Bauer, in the same year (1909), could not corroborate Marmorek's claims. He thought that though there might be "tuberculo-toxin" in the blood serum, sufficient amount could not be brought into test tubes

[3] Several articles have appeared in the United States since this paper was written. See *Addendum* at end of this paper.

for reaction by common methods. Bergeron (1911) raised serious objections to Marmorek's technique because the latter did not titrate complement; also, according to him, one-fifth increase in dose of amboceptor would change results from 90 per cent positive to all negative.

Although Marmorek's experiments might have been faulty, the antigen or toxin for which he tested resembled the Wildbolz antigen in that it may be produced anywhere in the body and finally excreted in the urine. This is in contradistinction to the work of Bruch (1906), Kurt Meyer (1908), and Débré (1911) (1914), who looked for antigen that was produced and secreted close to the point from which they collected their pathological fluid.

The work of Débré and Paraf (1911) (1914) is of interest. They attempted the search for tuberculous germs or special substances emanating from the bacilli in the serous or purulent effusions, or in the more general fluids or tissues that were washed by toxin. By their antigen reaction, which was one of complement fixation, they also tried to diagnose renal tuberculosis by searching for antigen in the urine.

Arloing and Biot (1914) searched for both antigen and amboceptor in sera and urines by complement fixation, using tuberculin and bacillary pulp as antigen in the search for amboceptor. They demonstrated that free amboceptor and antigen may be present simultaneously in the serum and urine.

Wildbolz (1919), believing that complement fixation was worthless because of the hemolytic or antihemolytic action of the urine, determined to use the skin test with the patient's own urine. No reaction resulted with the unconcentrated urine. He finally was successful by using morning urine concentrated to 1/10 its original volume by heating to from 65° to 70°C. in a vacuum and filtering out the urinary salts through filter paper treated with 2 per cent carbolic acid. He injected intracutaneously enough material to cause a bleb 5 mm. in diameter and used 1/1,000 and 1/10,000 Old Tuberculin to detect anergic individuals. He tested the same phenomena on persons affected with other diseases, including syphilis, typhoid fever, appendicitis, and leprosy; also on many normal persons. The leprosy case was the only one to give a positive reaction.

Imhof (1920) confirmed most of Wildbolz's results. In addition he introduced the auto-blood reaction, which he claimed was of great importance in cases exhibiting renal inefficiency. He took 10 cc. of blood from the arm and slowly added to it 200 cc. of 90 per cent alcohol. He

then brought the mixture to boiling for one or two minutes on the water-bath, after which he filtered. The filtrate was concentrated to 10 cc., again filtered, and then injected intracutaneously. Serum alone caused no reaction, indicating that the antigen was absorbed by the red cells. In two cases of renal tuberculosis, in which the auto-urine was negative, the auto-blood test was positive. With healthy individuals Imhof obtained negative results.

Offenbacher (1920), on the other hand, was not so successful with the test. He tried the reaction in 20 cases of active tuberculosis. Only three gave positive reactions. He believed that positive tests indicated active tuberculosis, whereas negatives had no significance.

Bressel (1920), after a study on a small series of cases, reported favorably on the value of the test as a diagnostic aid. In each of 32 pulmonary cases of demonstrable activity there was a positive auto-urine reaction. But in order to determine the real value of the test in diagnosis, he tried it on 15 patients who were suspected of tuberculosis, but whose active infection the clinical findings could not verify. In two the auto-urine reaction was negative, while the test with Old Tuberculin was strongly positive; in the other thirteen the reaction was positive. These results were confirmed later by repeated X-ray and clinical examinations. Therefore he decided that the reaction was very important as confimatory evidence in doubtful cases. He also found that the reaction generally corresponds to the extent of the tuberculous involvement. He tried the reaction on only two control cases. These were negative as to reddening and infiltration, although the Old Tuberculin injections were positive.

Reinecke (1920), however, adhering closely to Wildbolz's instructions, found no difference between the reactions of tuberculous and healthy individuals. He also found patients with poor allergic response giving strongly developed auto-urine reactions. He attributed the reactions to high salt content. His NaCl determinations on the concentrated urines averaged 9 to 10 per cent, in certain cases as high as 13 per cent. Reinecke's study was made on 45 pulmonary cases and 35 controls.

Lanz (1920) considered the reaction useful, although it gave positive results with two cases of congenital syphilis and with six nontuberculous cases. He found that the phosphates of the urine were the cause of the necrosis, although urea, oxalate, and hypertonic salt solution could cause skin reactions. Uric acid and urates were precipitated out by concentration. He learned that the Wildbolz reaction persisted for a long time

after healing, as determined by clinical and X-ray methods. But once there was a definite fibrosis and arrestment, the Wildbolz reaction became negative.

Eliasberg and Schiff (1920), after studying the test on 40 children, could not confirm the statements of Wildbolz in every particular but thought that the method was worth using. It is important to note that children with negative Old Tuberculin reactions also gave negative auto-urine reactions even if positive urines were injected. Their investigations appeared to show that the reaction was not an absolute criterion of activity in a tuberculous focus.

Ichok (1921), on account of the great divergence of opinion on the value of the reaction, sought to give incontestable biological proof that the urine excreted by the kidneys of a subject having active tuberculosis can contain a tuberculous antigen. He injected three rabbits with varying doses, never more than 2 cc. at a time, of urine supposed to contain tuberculous antigen. After six to eight months he was able to detect specific tuberculous amboceptor in two of the rabbits by means of the complement-fixation reaction, using Besredka's antigen. He also used the necessary increased doses of complement for rabbit serum, as suggested by Kolmer (1916).

His articles also contained many important suggestions that should be kept in mind in the use of the Wildbolz test. In addition to the possible occurrence of nonspecific skin reactions due to the salts, he mentions four other possibilities; (1) the presence of toxic substances in the urine of all tuberculous patients, (2) the excretion of special disintegration products of unknown composition in the urine of patients with lardaceous disease, (3) the elimination of living or dead bacilli in the urine of phthisical patients, apart from gross lesions in the kidneys, and (4) the presence of casts, cellular and bacterial elements (secondary microörganisms) in the urine of cases with genitourinary disease. He also points out the inadvisability of injecting the urine of patients whose condition is complicated with genitourinary disease, because the temperature for concentration *in vacuo* is not enough to bring about sterilization.

Von Bergen (1921), in an interesting paper, reported that the specific body in the Wildbolz auto-urine reaction is a heat-resisting, partly dialyzable, alcohol-soluble, biuret-free substance belonging to the tuberculin group. He found that the urinary antigens could be heated to 120°C. for one-half hour without changing their biological character-

istics. It seemed, in fact, that the specific reaction appeared more clearly with strongly heated than with weakly heated urine.

He also pointed out that many of the failures in the use of the auto-urine test might be due to faulty method of concentration. In addition to the distilling flask, he arranged first a Liebig condenser, second, a receptacle in the form of a graduated water bottle, then a manometer before the vacuum pump. Though there is hardly any necessity for all this apparatus, with his equipment no antigen will be lost by the urine boiling over and being drawn down the waste pipe connected with the vacuum pump.

Gramen (1920) tested 50 cases of tuberculosis and several healthy persons. He found the reaction positive not only in the active, but also in several healed and healthy cases. Half of the healed cases of surgical tuberculosis were weakly positive and half negative.

Bezançon (1921) found the method of Wildbolz of little value because of the great difficulty in reading the reaction. He also thought that the reaction depends to some extent on certain receptive factors of the patients, because the same sample of urine acted positively, negatively, and doubtfully in different patients.

Bosch (1921) applied the Wildbolz reaction to 220 subjects, including surgical, several lung patients, and 92 nontuberculous controls. Although his results did not confirm Wildbolz's statements in every particular, they were very encouraging. Of 56 tuberculous bone or joint cases, 36 were definitely positive, 12 weakly positive, and 5 questionable, while 2 were negative with an accompanying weak Old Tuberculin reaction, and one negative in an anergic individual. Of 20 respiratory cases, 11 were definitely positive, 2 questionable, 4 with weakly positive reaction accompanying a weak Mantoux reaction; 3 were negative, one being an anergic individual, the other two exhibiting weak allergic phenomena. Of the 92 nontuberculous cases, 73 had negative auto-urine reactions, although 22 were anergic as determined by the Old Tuberculin controls; 14 others had doubtful reactions; there was also one weakly positive in an allergic individual, and 4 weak positives in anergic individuals. The last four cases mentioned must have their reactions attributed to the non-specific salt factor. Five particularly interesting cases were those showing a positive auto-urine reaction, which disappeared a short time after surgical dissections of the tuberculous foci.

Bosch also found the reactions stronger in the earlier cases, thereby adding value to the test as a diagnostic aid. He then attempted to

lessen the salt concentration by adding 19 parts of 90 per cent alcohol to one of the concentrated urine. He learned that the antigen is alcohol-soluble and remains undamaged by his method of purification.

Gibson and Carroll (1921), using Wildbolz's technique, obtained favorable results in a study of 40 cases.

Schmid (1921), from his study of Wildbolz's technique on 150 cases, concluded that the reaction is valuable in determining active tuberculosis, if first, repeated injections at various periods are made in negative cases; second, if we can determine the active cases having persistently antigen-free urines; and thirdly, if we can exclude necrosis by making the urine salt-free without changing the antigen. In 60 patients proved definitely tuberculous by surgical, histological, or bacteriological method he obtained 49 positive and 11 negative reactions. Three of the 11 negative cases became positive on subsequent injections, one after 3 months, a second after 5 months, and the last one month after the negative reaction. Clinically all cases were retrogressing. In another group of 91 cases in which diagnosis could not be decided so accurately, he obtained 46 positive and 45 negative reactions. Although there were some exceptions, these results corresponded closely with clinical findings. Necrosis at the site of injection was noticed three times.

Čepulič (1921) aimed first to demonstrate with certainty the presence of a specific body excreted in the urine of patients with active tuberculosis. He injected, after first cooling and filtering urine through 2 per cent carbolic-acid filter paper, 0.2 cc. of the concentrated urine of an active case subcutaneously into a patient. Inside of 24 hours the patient exhibited great uneasiness, headache, great exhaustion, and focal reaction recognized through the increased physical signs, coughing and slight hemoptysis lasting two days. No reaction appeared at the injection point. In a control injection with a normal concentrated urine, neither a focal reaction nor systemic disturbance was caused.

He also determined that the concentrated sterile antigen would remain unchanged in the cold room as long as two to three weeks, perhaps longer.

In order to attain success with the Wildbolz test, Čepulič deemed it necessary to control the allergic response of individuals with intracutaneous injection of the partigens of Deycke and Much. He thought that single partigens, against which the body was not allergic, might be excreted in the urine. Unless we know of this specific anergy a false negative would be reported.

Farago and Randt (1921), after a study of about a hundred cases, concluded that the Wildbolz reaction appears positive when using urines from healthy individuals as well as those from tuberculous patients, probably due to the chemical and traumatic reaction of the concentrated salts. He also tested for the specificity of the tuberculous antigen in urine by injecting intracutaneously a tuberculous guinea pig as well as a healthy one with concentrated normal urine, concentrated tuberculous urine and Old Tuberculin. In the tuberculous animal all injections produced a positive local reaction, while in the healthy animal only the Old Tuberculin was negative. This proved the nonspecificity of the concentrated urine reactions. However, they did not carry out experiments in which the salt factor was ruled out.

Trenkel (1921) thinks that the determination of tuberculo-toxin circulating in the body would be a great step forward in determining "activity." This last term to him means fever, loss of appetite, gastro-intestinal disturbances and pulse-rate increase. He states "These are all caused by a tuberculo-toxin," so therefore he defines "activity" as "a condition that exists as long as a tuberculo-toxin is poured out from a focus of infection." He found positive reactions when using normal as well as tuberculous urines, and also in two far advanced anergic cases. With the urine of healthy patients exhibiting allergic conditions, he obtained 6 positive and 2 negative reactions. He decided that the two negative cases were due to low specific gravity urines, because a few days later more concentrated urines of the same patients gave positive reactions. Therefore he concluded that the reaction was chemical in nature, and of little use in diagnosis.

Alexander (1921) reported that, although a negative intracutaneous urine reaction does not exclude an active tuberculous process, a positive reaction indicates that activity is very likely present. He found that urines concentrated at 100°C. gave weaker reactions than the same urines concentrated by the Wildbolz method.

Liebhardt (1921) found 15 positive and 3 negative Wildbolz reactions in a study of 19 active tuberculous patients. Eleven nontuberculous subjects were negative. He was unable to demonstrate the antigen by complement-fixation methods. He considered the reaction in the present form impracticable on account of its too slight intensity and because of its inconstancy.

From this review of the literature it is seen that very little has been done on the more fundamentally scientific problems connected with the

subject; also that the views of various authors on the clinical value of the test are very different. Several believe that the positive reaction clearly indicates active tuberculosis; a negative result inactivity. Some find that certain active cases react negatively, while others report many nontuberculous cases reacting positively. As would be expected from the intracutaneous injection of a one-tenth concentrated urine, many authors report nonspecific reactions of a traumatic or osmotic nature due to high salt content.

II. EXPERIMENTAL PART

1. Clinical application of Wildbolz's original reactions

Because of the great divergence of opinion on the clinical value of the test, it was deemed advisable to add another report to this phase of the subject. This study offered an opportunity to partly explain the variance of views expressed by the different authors.

Great care was taken in the preliminary chemical and microscopic examinations of each urine, so that those showing signs of renal infection would not be used for intracutaneous injection. Wildbolz's instructions were followed closely. One hundred and fifty cubic centimetres of freshly collected morning urine were placed in a 500 cc. filtering flask. This receptacle was attached by pressure tubing to an electric vacuum pump capable of maintaining from 25 to 28 inches of vacuum. A tight-fitting rubber stopper holding a thermometer was inserted in the neck of the flask. After the vacuum pump was started the filter flask was placed in a water-bath kept close to 100°C. Care was taken that the temperature of the urine did not go above 60°C.

When the urine was concentrated to 15 cc., it was allowed to cool and filtered through sterile filter paper. Five-hundredths cubic centimetre of the filtrate was injected intracutaneously in the forearm of the patient who produced the urine. An inch and one-half below the site of this injection 0.05 cc. of a 1/1,000 dilution of Old Tuberculin was injected in the same manner.

Although 0.05 cc. of inoculum was used in the tests, it was soon found that a wide range in the skin reactions resulted. Some patients gave a definite zone of reddening around the point of injection; others presented only a hardening at this point; while still others gave both the hyperemia and induration of different degrees. The proper appreciation of these various kinds of reaction is very difficult and it is very probable that many

of the discrepancies in the results of previous investigators have been due to different standards which have been adopted as to reaction significance.

Due to the great difficulty in interpreting the skin reactions, it was found necessary to carry out an extensive preliminary study on many cases, using as controls concentrated normal urine and salt solution. From this preliminary study it was learned that nonspecific reactions often appear either immediately or after two to four hours, and persist rarely after forty-eight hours. The specific tuberculin-like reactions of the urine lasted from three to fourteen days. These reactions were called specific because of other evidence furnished in antigen-purification studies, which will be presented later.

It must be noted that urine reactions which persisted after forty-eight hours were much less intense than 1/1,000 and, in many cases, less than 1/10,000 Old Tuberculin reactions. The majority of reactions presented a 5 mm. zone of infiltration or hyperemia or both, while many gave a

TABLE 1

CLASSIFICATION	TOTAL	+++	++	+	?	−
Far advanced	29	3	12	5	5	4
Moderately advanced	31	2	12	8	4	5
Borderline cases	25	2	7	2	4	10
Normals	18	0	0	1	1	16

zone of 3 mm. Very rarely a reaction of 7 mm. persisted after forty-eight hours. In the records the sign + was used to designate 3 mm. zones, ++, 5 mm., and +++, 7 mm. diameters. Any induration or reddening of less than 3 mm. diameter was designated by ?, and complete failure to react by −.

After the adoption of this standard, the original Wildbolz test was applied to the urine of 103 individuals, including 29 far advanced tuberculous cases, 31 moderately advanced, 25 "borderline" or suspicious cases, and 18 normals. The results obtained will be seen in table 1.

If the Wildbolz reaction is to be of practical value, it must be of the greatest aid in the "borderline" cases, that is, those patients whose suspected tuberculous activity can not be definitely diagnosed by the means now at our disposal. Although this clinical application study was not emphasized, it is possible to report some interesting facts relating to the clinical status of these "borderline" cases. After a month to a month and a half of clinical study of these patients in an observation

ward, 11 of the 25 cases were diagnosed "active." Of these eleven, 7 had given a positive Wildbolz and 4 a negative. On the other hand, of the 14 who had been diagnosed "No manifest tuberculosis," 6 had a positive Wildbolz and 8 negative reactions.

Due to the small number of cases studied, no extensive conclusions are to be drawn from this investigation. However, it should be said that although Wildbolz's contentions are not confirmed in every particular the results tabulated above are such that the Wildbolz reaction should receive more attention, particularly in this country.

Reasons for divergence of opinion on the value of the test: It seems certain that the high salt content of the one-tenth concentrated urine must be removed before the test attains any practical significance. The great

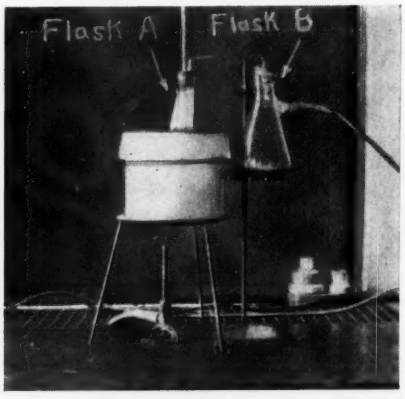


FIG. 1

divergence of opinion among the previous authors is undoubtedly due chiefly to the high salt factor. Personal equation enters strongly into the reading of the reactions. Even long experience with the original technique will not bring the required proficiency in interpreting results.

Then also, the technique used will probably partly account for the different results reported. Some authors report using 0.05 cc., others 0.1 cc. inoculum. The latter dose of a concentrated urine for intracutaneous injection seems too large. Five-hundredths cc. of urine causes a bleb of 5 mm. diameter if injected properly, and causes much less nonspecific reaction than a 0.1 cc. dose. The production of the 5 mm. bleb seems to be the best indication of the proper dose and also correct injection technique. No areas of necrosis were seen in this study, but many papers report that a too superficial injection will result in necrosis.

Another cause of disparaging results might be traced to the nature of the apparatus advocated by Wildbolz. It was learned from this study that a 500 cc. filter flask directly attached to the vacuum tubing would allow some of the solid constituents of the urine to escape if the temperature of the water bath and the vacuum pressure were not watched closely. Antigen if present in the urine would no doubt be lost in this manner. Von Bergen called attention to this defect and remedied it. The need for all his modifications cannot be seen from this study. However, it was found necessary to add one more flask (as shown in fig. 1) to the apparatus of Wildbolz.

Flask B in many experiments showed only pure condensation water, which could be thrown away. But whenever the urine in A was drawn over to B, it was poured back into A and exposed to more careful vacuum concentration. The concentrated urine in A was then submitted to the further steps of Wildbolz's technique. (See fig. 1.)

2. Purification of urinary antigens

As it was the main purpose of this paper to acquire more definite information about the chemical, physical, and biological properties of the antigens excreted in the urine of active tuberculous cases, an early attempt was made to obtain antigen in a relatively pure and concentrated form. Then too, tuberculous antigen freed from the high concentration of urinary salts and other nonspecific substances would in all probability lead to more easily interpreted skin reactions, as well as to a preparation which could be detected by complement-fixation technique.

Due to the large number of heterogeneous chemical substances in urine the purification of a tuberculous antigen, about the nature of which little is known, is an extremely difficult task. Von Bergen (1921) has found the antigen to be a heat-resisting, partly dialyzable, alcohol-soluble, biuret-free substance of the tuberculin type. Bosch (1921) confirmed the alcohol-soluble nature of the material, while a few others have defined antigen as diffusible without any definite mention of their dialyzing method.

Although there are present in urine many widely different chemical substances ranging in complexity from the inorganic salts to protein, dialysis seemed to offer the most hopeful basis for any process of purification. While experiments to produce collodion sacs of the proper permeability were being made, preliminary diffusion studies were carried out with parchment paper.

The method of antigen purification and concentration advocated by Wadsworth (1921) seemed to be well suited for the problem at hand. He applied his method to various extracts of tubercle bacilli, in order to obtain a more sensitive antigen for complement-fixation work. He found that when water and glycerin extracts were submitted to the following procedure their power was enhanced greatly: The extract of antigen was first dialyzed for five days, then one part of horse serum to twenty parts of extract was added. Next, the globulins were precipitated by passing carbon-dioxide gas free from hydrochloric acid into the solution for one-half hour, at 37°C. The precipitated globulin which had carried down the antigen by absorption was extracted with alcohol. The alcoholic solution was evaporated to dryness *in vacuo*, and the residue taken up in NaCl (0.85 per cent) solution.

This technique was applied to the urinary antigen in the following manner: After 500 cc. of urine from a patient presenting a strong autogenous urine reaction was reduced *in vacuo* to about 35 cc., the precipitated urinary salts were filtered out. The residue on the filter paper was washed with three separate portions of distilled water until the filtrate reached 50 cc. volume. This concentrated urine was submitted to five days' dialysis in running water. In the first experiments a parchment paper bag was used; in the later studies collodion sacs were employed entirely. At the end of five days the dialyzing residue was decreased to its original volume *in vacuo*. One-half of this product was preserved to test for antigen, both by the intracutaneous skin test and by complement fixation. The other half was subjected to the added steps of purification advocated by Wadsworth. After the alcoholic extract of antigen adhering to the precipitated protein had been obtained it was evaporated to dryness *in vacuo* and the residue, which was invisible, was taken up in 25 cc. physiological saline solution. The preserved portion of the dialyzing residue was tested for the presence of sodium chloride and urea. No trace of either was found. This aqueous solution of antigen was evaporated to dryness *in vacuo* at a temperature of less than 60°C. The invisible residue which resulted was then taken up in physiological saline solution, so that it would have no nonspecific osmotic effect in subsequent intracutaneous injections.

Finally, 0.05 cc. of both of the above preparations were injected intracutaneously into the forearm of an allergic individual. There was a definite circumscribed area of induration and reddening, 7 mm. in diameter, where the product of dialysis alone was injected. This reaction remained

on the arm for two weeks. At the site of the injection of the product obtained by Wadsworth's complete method, an area of redness 3 mm. in diameter appeared. This reaction lasted for ten days, while the saline control reaction disappeared within twenty-four hours.

This method of testing for the presence of antigen was next checked up by the complement-fixation method. The saline solutions of both preparations were carefully titrated for their anticomplementary dose. One-fourth of this quantity (0.2 cc.) was mixed with 0.2 cc. doses of 10 known tuberculous amboceptor sera and 4 normal sera inactivated at

TABLE 2

Complement fixation tests for tuberculous urinary antigen after five days' dialysis and also after Wadsworth's complete method of partial purification

SERUM NUMBER	MILLER ANTIGEN	PETROFF ANTIGEN	TUBERCULOUS URINE AFTER DIALYSIS	TUBERCULOUS URINE AFTER WADSWORTH'S METHOD	NORMAL URINE DIALYZED	NORMAL URINE WADSWORTH	CLINICAL DIAGNOSIS
2719	++	+++	++	++	−	−	Moderately advanced active
2731	−	−	−	−	−	−	Normal
2730	+++	+++	+++	+	−	−	Far advanced active
2725	++	+++	++	++	−	−	Far advanced active
2732	+++	++++	+++	−	−	−	Moderately advanced active
2733	+−	−	−	−	−	−	Normal
2028	−	−	−	−	−	−	Normal
2734	+++	++++	+	−	−	−	Moderately advanced active
1577	++	++++	++++	++	−	−	Moderately advanced active
2141	++	+++	+++	++	−	−	Far advanced active
2365	++	++	+++	++	−	−	Moderately advanced active
2050	+	+++	+	−	−	−	Moderately advanced active
2697	+++	++++	+++	+	−	−	Moderately advanced active
2687	−	−	−	−	−	−	Normal

56°C. for thirty minutes. Two units of guinea pig complement (pooled from five guinea pigs) were added and the mixture incubated in a water bath at 37°C. for one and one-half hours. After this incubation the hemolytic system, consisting of 1 cc. of 2.5 per cent sheep cells and two units of rabbit antisheep amboceptor, was added. The total volume in each tube was 3 cc. One-quarter of the anticomplementary dose of Petroff glycerin-extract antigen and also Miller's antigen were used as controls of the amboceptor content in the sera, while a mixture of three normal urines subjected to the same procedure as the antigenic urines was also used as a control.

It is seen from table 2 that antigen can be detected in concentrated tuberculous urine more definitely after five days' dialysis than after the application of Wadsworth's complete method. The results obtained in the intracutaneous reactions of allergic individuals also point to the presence of a greater quantity of antigen in the dialyzing residue.

Practicability of dialysis in modification of Wildbolz reaction: If the period of dialysis could be materially decreased this method might be made of such a practical nature that it could be used to free the concentrated urines of the troublesome salt factor. From a theoretical viewpoint, it seems that the antigenic urine should be freed from all its inorganic and organic constituents except the antigen, so that the latter after evaporation to dryness could be taken up in the proper quantity of salt solution (0.85 per cent). As urea among the organic compounds and sodium chloride among inorganic salts constitute the bulk of the urinary solids, and also because they are readily determined quantitatively, the following experiment was carried out to learn whether a salt and urea-free urine could be obtained within five hours and, if not, within twenty-four hours:

Three hundred and seventy cc. of strongly antigenic urine from an active pulmonary case of tuberculosis was concentrated *in vacuo* to one-tenth volume. After cooling, this concentrated urine was filtered through paper. The residue was washed with distilled water until the filtrate was brought to 37 cc. volume.

One cc. of the filtrate analyzed for chlorides by the Volhard method showed the presence of 9.6 per cent NaCl; and 0.5 cc. of a 1/10 dilution analyzed for urea by the Van Slyke method gave 13.8 per cent urea.

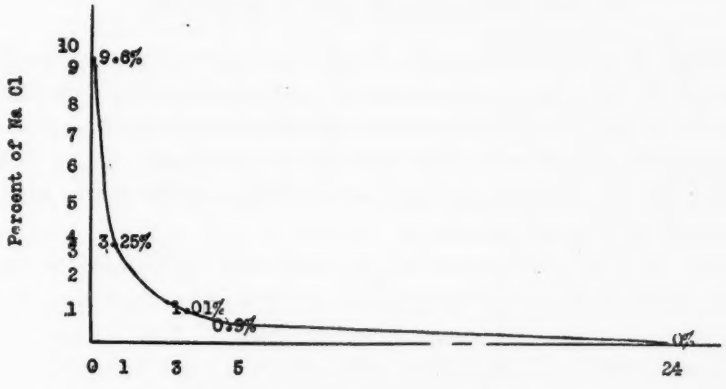
Thirty-five cc. of the filtered concentrated urine was placed in a dialyzing bag in running water for twenty-four hours. At the end of one, three, five, and twenty-four-hour periods, 1.0 cc. were used for NaCl and 0.5 cc. for urea determinations. The increased volume of the dialyzing residue, as well as the amounts removed for chemical determinations, were considered in the calculations of NaCl and urea present, thereby placing the results on an equal basis.

Charts I and II illustrate the results obtained.

Of course the quantities of urea and sodium chloride vary considerably in different urines from the same patient, as well as those from various individuals, but, nevertheless, several like experiments on many urines have shown that the accompanying curves present a fairly accurate picture of the NaCl and urea content of the dialyzed concentrated urine.

CHART I.

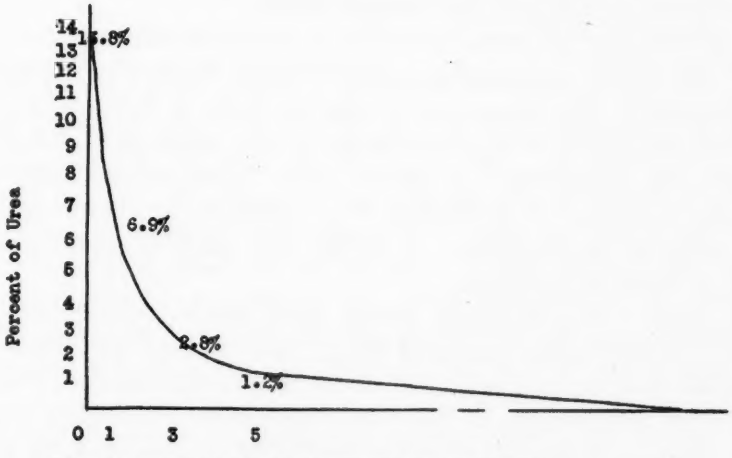
SHOWING DECREASE IN Na Cl CONTENT OF URINE BY DIALYSIS.



Time in hours at which determinations were made.

CHART II.

SHOWING DECREASE IN UREA CONTENT OF URINE BY DIALYSIS .



Time in hours at which determinations were made. 24

It is very probable that all of the chloride and urea disappear before 24 hours, but no other determinations were made after five hours, because the amount of work required before and after dialysis necessary for the preparation of the antigen would prevent the injection of the material on the same day.

3. The use of collodion sacs in purification

Although success in freeing the Wildbolz antigen from the inorganic and most of the organic substance of many urines was obtained by the use of a parchment membrane, collodion sacs have many advantages over the parchment. The porosity of parchment varies greatly, whereas collodion sacs of uniform permeability can be made with the proper skill and technique.

The results of the earlier part of this work with the parchment dialyzing bag showed that the tuberculous antigen was weakened due to partial diffusion, thereby confirming the work of Von Bergen (1921) and Ichok (1921). A collodion tube which is less permeable than the parchment was needed.

Qualitative tests showed that the parchment permitted a rapid diffusion of sodium chloride, glucose, and urea; whereas it allowed only the slightest trace of dextrin to diffuse in 24 hours. The parchment was impervious to starch and serum-albumin.

In order to find the proper procedure for the preparation of collodion sacs of the proper permeability, considerable preliminary experimenting was necessary. The important systematic study of Brown (1915) on collodion membranes helped materially in this phase of the work, as did also the contribution of Gates (1921). The valuable discovery of Brown's method of preparing dried collodion membranes treated with different concentrations of alcohol was used to produce membranes of different porosities.

The method of preparation finally used was as follows: A paper collar two inches high was fitted snugly three-fourths inch down into the necks of six scrupulously cleaned and dried test tubes (6 x 1 inch). Twelve per cent solution of collodion (obtained by evaporating a solution consisting of pyroxlin 4 grams, alcohol 25 cc. and ether 75 cc. to one-third volume and testing by the viscosometer method of Gates) was poured into each tube up to a point just a little above the lower border of the paper collar. The collodion was allowed to remain in the tubes until all air bubbles had come to the surface. The tubes were

then stood neck downward in a rack to drain for five minutes. After this, air was blown into the tubes until they were partly dry. They were then filled with distilled water and allowed to stand for an hour. After this, they were emptied and turned neck downward in a wire basket and placed in the incubator at 37°C. to dry completely. When the membranes came in contact with the water they took on a dense opacity, which entirely disappeared on complete drying.

The dried membranes adhering to the test tubes were then ready for the important alcoholic treatment. Each of the six tubes was filled respectively with 70, 75, 80, 85, 90, and 95 per cent (all by volume) alcohol. After 24 hours the alcohol in each tube was replaced with distilled water. The water was allowed to remain in the tubes for about two hours. The collodion membranes were then separated

TABLE 3

Showing NaCl content of various sacs after dialyzing 6.5 per cent NaCl solution in running water for 30 minutes

SAC	PER CENT OF NaCl IN DIALYZING RESIDUE BASED ON ORIGINAL VOLUME	VOLUME IN SAC AT 30 MINUTE PERIOD
per cent	*per cent*	*cc.*
70	6.45	22.3
75	5.8	23.0
80	4.1	26.0
85	2.7	26.0
90	1.6	26.0

from the tube by first loosening the paper collar with a scalpel and then blowing water between the membrane and the tube wall. After some practice this last step can be done with ease and rapidity.

Although membranes made inside test tubes are thinner and more fragile than those made on the outside of tubes, it was found that all the collodion sacs produced by the above method, with the exception of the one treated with 95 per cent alcohol, were sufficiently durable for the handling to which they were subjected. The 95 per cent membrane was extremely fragile, and moreover it had a strong tendency to shrinkage, thereby introducing an objectionable factor.

Permeability tests: The following experiment was carried out to determine the relative rapidity with which a 6.5 per cent NaCl solution diffuses through the different membranes. The five sacs were strung out several inches apart in a large vessel of running water. Twenty cc.

of the 6.5 per cent NaCl solution were placed in each sac and subjected to dialysis for thirty minutes. At the end of this period the volume of the dialyzing residue was noted and 2 cc. analyzed for NaCl.

Table 3 readily shows that the higher the concentration of alcohol with which uniform, completely dried collodion sacs are treated, the more rapid is the diffusion of sodium chloride. However, an experiment of this nature does not give complete information about the permeability of the different sacs; as has been noted by Gates, "The sodium chloride molecules . . . . are of relatively small size, and the rate at which they diffuse through permeable membranes suggests that the pores of the membrane must be several times the size of the molecules to permit such rapid passage."

TABLE 4

Showing diffusibility of chemicals of different complexities in the various sacs

DRIED SACS TREATED WITH	ALCOHOL				
	70 per cent	75 per cent	80 per cent	85 per cent	90 per cent
Sodium chloride	+	+	+	+	+
Glucose	+	+	+	+	+
Urea	+−	+	+	+	+
Dextrin	−	−	−	+−	+
Starch	−	−	−	−	−
Serum-albumin	−	−	−	−	−

+ means diffusion takes place in 24 hours.
− means no diffusion takes place in 24 hours.
+− means very little diffusion takes place in 24 hours.

More complete information about the permeability of the different sacs was next sought by dialyzing chemical substances of different complexities in standing water and testing the dialysate after 24 hours for the evidence of diffusion. All the alcohol-treated collodion membranes were permeable to NaCl, glucose, and urea. The 70, 75, and 80 per cent sacs were impervious to erythro-dextrin, and the dialysate of the 85 per cent sac gave only the faintest trace of erythro-dextrin with tincture of iodine. The 90 per cent membrane was more permeable to the dextrin, but allowed no diffusion of starch or serum-albumin.

The experiment showed that the permeability of an 85 per cent sac most nearly approximated that of the parchment which was used in the earlier part of this work. As the tuberculous urinary antigens

were partly diffusible in sacs of this permeability, the sac treated with a lower per cent alcohol, which would be permeable to urea chiefly, should be the logical choice for the purification process. It should be mentioned here that it cannot be expected that diffusion of concentrated tuberculous urines in a semipermeable membrane will leave the antigen in pure form in the dialyzing sac. Although diffusion may separate out the familiar products in the urine, such as the inorganic salts, urea, creatinine, uric acid and the purine bases, there are also present more complex substances which are usually classified under "undetermined nitrogen." Salkowski (1905) (1910), Bondzynski (1905), and Ginsberg have called attention to those colloidal alcohol-insoluble nitrogenous products, whose quantities are increased in certain diseases. Additional steps of purification must be added if these and other complex molecules, such as the Bence-Jones bodies, the urinary pigments, and albumin are to be removed from the antigen. However, it is probable that for our purposes freeing the specific antigen from these products will not be necessary.

The next important step was to test the diffusibility of urea in the five membranes mentioned above. The following experiment was designed to show the quantity of urea left in the dialyzing residues after 18 hours' dialysis in running water: Fifteen cc. of a 15 per cent urea solution (the average concentration of urea in several urines concentrated to one-tenth volume) was placed in each of the sacs strung out as in the preceding experiment. After 18 hours the volume of each dialyzing residue was noted and 0.5 cc. quantities of each sample were analyzed by the urease method of Marshall, Van Slyke, and Cullen for the urea content. No urea remained in the sacs treated with 80, 85, and 90 per cent alcohol, while the 75 per cent sac contained 1.85 per cent and the 70 per cent sac 14.8 per cent urea based on the original volume of 15 cc.

Table 5 clearly illustrates the results of this experiment.

The fact that the 80 per cent sac retained dextrin and allowed urea to entirely diffuse out in 18 hours pointed to its choice as the sac of proper permeability. However, several dialyzing experiments were carried out, in which urines concentrated to one-tenth were used, with the result that the 70 and 75 per cent sacs had to be definitely excluded because they retained so much of the organic constituents of the urine. After this, many experiments were conducted in an effort to determine how the 80, 85, and 90 per cent membranes behaved toward the

antigenic substance of urines from active tuberculous patients. The first experiment of this nature is fairly representative of other similar investigations and will be reported in detail.

Two hundred and fifty cubic centimetres of urine from an active tuberculous patient, free from albumin, Bence-Jones bodies, and all microscopic evidence of kidney involvement, were concentrated *in vacuo* to 20 cc. This was thoroughly cooled and filtered through paper. The residue was washed with distilled water which was allowed to pass into the filtrate until a 25 cc. volume was reached. Then 5 cc. of this filtrate were placed in 80, 85, and 90 per cent sacs and allowed to diffuse in running water for 24 hours. At this time no trace of sodium chloride or urea remained in either dialyzing residue. The residues were concentrated to dryness *in vacuo* and taken up in 5 cc. of NaCl (0.85 per cent)

TABLE 5

Showing urea content of various sacs after dialyzing 15 per cent urea in running water for 18 hours

SAC	PER CENT OF UREA IN DIALYZING RESIDUE BASED ON ORIGINAL VOLUME	VOLUME IN SAC AT END OF 18 HOUR PERIOD
per cent		*cc.*
70	14.8	17.5
75	1.85	19.0
80	0.0	17.0
85	0.0	16.0
90	0.0	15.5

solution. Five hundredths cc. of each sample was injected intracutaneously 1½ inches apart on the forearm of an allergic individual. This experiment resulted as follows: From the second to the fifth day the material from the 80 per cent sac showed a typical tuberculin-like area of inflammation of 7 mm. diameter, that from the 85 per cent sac an area of 3 to 4 mm. diameter, and the material from the 90 per cent sac caused no reaction whatever.

Von Bergen and Ichok, and the writers in the earlier part of this investigation, demonstrated that the antigenic substance was soluble in alcohol. As Bondzynski and others have called attention to colloidal nitrogenous products that are insoluble in alcohol, the presence of these substances was next tested, as was also the presence of the specific antigenic substances in the alcohol-soluble fraction. In order to do this, the technique of the preceding experiment was followed down to the point where the various dried residues of portions remaining

in the three sacs were obtained. Then 20 cc. of alcohol (97 per cent) were added to each residue. Practically no insoluble material was observed in the sample from the 90 per cent sac, only a faint trace in that from the 85 per cent sac, but a definite and relatively marked amount in the material from the 80 per cent sac. Each of the flasks to which the alcohol had been added was shaken vigorously from 20 to 30 minutes, and then filtered through paper. The insoluble residue of each flask was exposed twice more to the same alcoholic treatment, and each time the alcohol was poured over the residue that remained in the filters, in order to obtain whatever alcohol-soluble material might be adhering to the insoluble precipitate. The alcohol-soluble fractions were concentrated *in vacuo* to dryness and taken up in 5 cc. of NaCl (0.85 per cent) solution. The three different samples were then exposed to the last step of the technique of the preceding experiments, that is, injected into an allergic individual. The same gradation of reactions resulted, although the material from the 80 per cent sac gave an area of reaction of only 5 mm. in diameter, while that from the 85 per cent sac exhibited a 3 mm. zone of reaction. No change occurred at the point of injection of the material from the 90 per cent sac.

From these diffusion studies with collodion sacs of different permeabilities a tangible feature of the physical properties of the antigen is brought out. The specific substance is held back by a semipermeable membrane which will retain erythro-dextrin, but will partly diffuse through one which allows the slow diffusion of the dextrin. The antigen will be entirely lost through a sac which permits diffusion of starch or serum-albumin.

After this work on the purification of antigen by dialysis was well under way, a very interesting paper appeared on a somewhat similar investigation. Lanz (1922) reported the use of collodion sacs to produce a salt-free isotonic urinary preparation for the auto-urine reaction. The method which he used to prepare sacs of the proper permeability is entirely different from that used in this work. He used apothecary's collodion, a commercial preparation made in Germany. His sacs were made on the outside of test tubes by dipping the latter in the collodion. After the dropping of the collodion had stopped he stood the tubes upside down to dry for one-half hour at room temperature. He repeated this dipping and drying process three times, then dipped for the fifth time and allowed the sacs to dry for one and one-half hours at room

temperature. The sac adhering to the test tube was then placed in water for five minutes. The upper edge of the collodion was cut and slipped off the tube. Its permeability was then tested with 2 per cent lactose or dextrin. It had to be impervious to these substances.

Lanz was chiefly interested in freeing the concentrated urine from inorganic salts; in the work reported in this paper urea and as many other of the nonspecific constituents of the urine as possible were kept in mind. He also made no mention of alcoholic treatment of the sacs, which was found in this study to be a much more important factor in permeability than was the thickness of the sacs.

4. Chemical nature of the antigen

The term *antigen* is usually defined as any substance which can stimulate antibody production. In the light of the work of Ichok, who was able to detect amboceptor in rabbits' serum after repeated doses of the tuberculous urinary active principle, the word *antigen* is rightly applied. However, attempts in this investigation to confirm Ichok's work were entirely unsuccessful. If antigen is described as a substance that will bind complement in the presence of its specific amboceptor, then our work would tend to substantiate the use of the term.

Theoretically, the antigen which Wildbolz detected in the urine of tuberculous patients could very well be the active principle which diffuses into the lymph and blood-stream surrounding the active focus of infection and incites the changed reactivity of the body tissues. Substances which would have this power have been very generally considered as proteins or protein-like. Many unsubstantiated claims have been made of the discovery of protein-free substances which had antigenic properties. Jacoby's (1901) work has been frequently cited. He digested commercial ricin for five weeks in trypsin solution. At the end of this time he obtained a ricin which still possessed antigenic properties, but gave no protein reactions.

Work by Osborne, Mendel, and Harris (1905) appears to have fully refuted Jacoby's claims. They found the purified ricin to be identical with the coaguable albumin of the castor bean, and that tryptic digestion destroys the characteristic ricin properties. During recent years claims have been made that nonprotein antigens have been demonstrated, but most authorities believe that the large majority of sub-

stances which have antigenic properties are proteins or protein-like substances.

The first part of the chemical work of this study was an investigation as to whether the Wildbolz antigens reacted to the common protein analytical tests. Five hundred cubic centimetres of urine from an active tuberculous patient were tested for the presence of Bence-Jones bodies or albumin by the heat test, Spiegler reagent, and Heller's test. As all reactions were negative, the urine was concentrated to 50 cc. *in vacuo* at less than 60°C. The concentrated solution was thoroughly cooled in the refrigerator for one hour. The precipitated materials were filtered off by paper and the filtrate placed in two 80 per cent collodion sacs to dialyze in running water for 24 hours. The dialyzing residues were concentrated *in vacuo* at less than 60°C. to dryness. The dried residues were taken up in 25 cc. physiological saline solution and tested for antigen by the Mantoux test in an allergic individual alongside of three injections of Old Tuberculin of the following dilutions: 1/1,000, 1/10,000, and 1/100,000. The urinary antigen injection gave a reaction similar to the 1/1,000 Old Tuberculin. An area of induration and reddening 10 mm. in diameter resulted and persisted for over three weeks.

Several of the common tests for protein were tried upon the antigenic material which at this time still contained small quantities of nonspecific colloidal nitrogenous matter, such as the urinary pigments and the proteic and oxyproteic acids of Salkowski and Bondyznski. In spite of the presence of these impurities in the antigenic preparation, the heat test, biuret, Spiegler's, Hopkin's Cole and xanthoproteic reactions were all negative. Salting out with various concentrations of $(NH_4)_2SO_4$ also gave no positive indication of the presence of the various protein fractions. Millon's test alone was positive, but, as this might be caused by many substances very different in composition from proteins, no conclusion can be drawn.

It should be valuable to know whether any of the biological characteristics of the antigen would be destroyed by digestion in pepsin or trypsin. These latter determinations would be important, not only in giving information about the protein nature of the antigen, but also from a practical viewpoint they would help toward a better understanding of the resistance of antigens in contact with the proteolytic enzymes that have been demonstrated in the tissues of the patient and also in his urine.

5. Resistance of the antigen to various physical and chemical agents[4]

The antigen proved to be very resistant. Autoclaving at 18 pounds pressure for 15 minutes, strong H-ion and OH-ion concentrations and pepsin and trypsin exerted no damaging influence as evidenced by subsequent skin tests. After remaining in the icebox three months the antigen still maintained its original potency.

The fact that the biuret, xanthoproteic, Spiegler's and heat tests on the antigen were all negative, and that pepsin and trypsin had no destructive influence on the active principle, would tend to rule out protein in the antigenic substance. However, great caution should be observed in making deductions from the above experiments. In the first place it is possible that the various qualitative chemical tests used were not delicate enough to detect the small amount of protein necessary to cause the biological skin reaction; and then again pepsin or trypsin, or both, might have broken down the protein, the proteose, peptone, or more complex polypeptids to more simple products that still exhibited an active property in an allergic skin. This latter presumption is suggested in the work of Abderhalden (1912), who obtained anaphylactic reactions with a 14-member polypeptid.

6. Nature of colloidal nitrogenous urinary products

Very little work of an exact nature had been done on the more complex nitrogenous products of urine. These substances, together with some amino acids, purine bases, partially oxidized fragments of protein molecules, and the urinary pigments, are usually classified in the nitrogen partition of the urine as undetermined nitrogen. The chemical nature of the more complex products in normal as well as pathological urines will probably be more or less indefinitely understood until better methods of purification are developed.

The urinary pigments have been studied to a certain extent. The first of these to be discovered and studied was urochrome, which is the principal pigment of the urine. It was discovered and named by Thudicum (1864), who described its properties. Urochrome is readily soluble in water and 95 per cent alcohol. It is less soluble in benzene,

[4] Due to the necessity of shortening this article the results on the above subject are reported only in summarized form. For more detailed information readers are referred to the original Ph. D. dissertation of the senior author in the Library of Yale University.

chloroform, and ether. Palmer and Cooledge (1914) believed that urochrome is identical with the yellow pigment (lactochrome) of milky whey.

Salkowski (1905, 1910) and others have studied the presence of non-diffusible nitrogenous products of the urine. Salkowski has applied the names *oxyproteic acid* and *alloxyproteic acid* to substances that are insoluble in alcohol. He found that they made up 3.5 per cent of the total nitrogen in normal urines, 8.9 per cent of the total nitrogen in certain diseased conditions, and 28.1 per cent of the total nitrogen of the urine from a case of acute yellow atrophy of the liver.

The amount of this colloidal nitrogenous material found by Salkowski in normal urines is about that of the unknown nitrogen present in the urine of an average adult. Ginsberg and Gawinski later confirmed this by finding that the total nitrogen of these substances ranged from 3.0 to 6.8 per cent of the total nitrogen of the urine of a man on a mixed diet. As the less complex nitrogenous compounds of undetermined nature were lost by diffusion through the 80 per cent collodion tube, a comparative study of total nitrogen of the alcohol-soluble and alcohol-insoluble portions of the dialyzing residues of many concentrated urines was undertaken. Specific tuberculin-like reacting substances of tuberculous urines were found to be alcohol-soluble; therefore, although solubilities of these complex organic substances are relative, the following experiment was carried out:

After the 35 cc. of the 80 per cent sac dialyzing residue from different urines were obtained as in the preceding experiment, 5 cc. were used for total nitrogen determinations in duplicate. Twenty cc. of the remaining dialyzing residue were evaporated to dryness *in vacuo* in a Kjeldahl flask. Then 20 cc. of ethyl alcohol (97 per cent) were added and the flask thoroughly shaken for one-half hour. The white precipitate which was formed was allowed to settle and the supernatant liquid filtered into another Kjeldahl flask. This technique of alcoholic extraction and filtration was repeated 3 more times. The small amount of white precipitate on the filter was washed back into the Kjeldahl flask containing the remainder of the alcohol-insoluble material. Both portions were then evaporated to partial dryness, and total nitrogen determinations made on each. In the early experiments of this nature, the total nitrogen determinations were done on the original dialyzing residue containing the combined alcohol-soluble and alcohol-insoluble parts, and then on both the fractions. The sum of the last two deter-

minations approximated with a fair degree of accuracy four times the original total nitrogen determination which was made on one-fourth as much material. The results of a few of these experiments on both urines from tuberculous and healthy individuals suggested the very interesting point that the quantity of alcohol-soluble substance was from 2 to 6 times that of the alcohol-insoluble fraction in tuberculous urines, while in normal urines the ratio of alcohol-soluble to alcohol-insoluble material was from 1:1 to 1:10. In addition to the increased relative amount of alcohol-soluble fraction of nitrogenous material that was held back by the 80 per cent tube in the tuberculous urines, there was usually an absolute increased amount of this fraction over that present in normal urines.

Several experiments on the relative amounts of alcohol-soluble and alcohol-insoluble total nitrogen in the dialyzing residues of the same tuberculous urine from the 80 and 85 per cent tubes suggested strongly that the alcohol-soluble portion of the colloidal material diffused through the 85 per cent collodion tubes. The ratio of the fractions of the tuberculous urines from the 85 per cent tubes resembled very closely that of normal urines. A few experiments have suggested the possibility of correlating the extent of skin reaction with amounts of alcohol-soluble nitrogen in the dialyzing residue of the different collodion tubes.

Chemical nature of the alcohol-soluble antigen: A relatively large quantity of alcohol-soluble material was obtained for further identification purposes. The alcohol was evaporated *in vacuo* and the residue taken up in a small quantity of distilled water. A creamy white opalescent suspension resulted. This gave no protein tests, not even Millon's which was positive in the less completely purified preparation of antigen. The test for organic phosphorus by means of molybdic acid in a nitric-acid medium was strongly positive. The antigen was insoluble in ether and acetone. The Salkowski test for cholesterol was negative. The results of the brief research into this phase of the work suggested that the alcohol-soluble antigen was a phosphatid, probably lecithin. Of course our methods for extracting lipoids from proteins are by no means perfect, so that the above statement is made with some reservation.

7. *Biological nature of the antigen*

Although many years have elapsed since Koch (1890) discovered tuberculin, there is still much confusion as to its nature, both chemical and biological. Although there seems to be little doubt at present

that the active principle of many tuberculins is protein in nature, many authors report tuberculin-like reacting substances in which no protein properties can be demonstrated. Only recently Long (1921) has reported that the filtrate of a culture on a synthetic medium having NH_4Cl as the sole source of nitrogen, when concentrated to one-fourth its original volume, acted as a potent tuberculin, but did not react positively to any of the standard qualitative protein tests.

Many authors have established rather firmly that tuberculins are not toxins, and that the reactions to tuberculin differ markedly in normal and tuberculous animals. Krause (1911) in this country injected 25 cc. of a filtered watery extract of *Mycobacterium tuberculosis* intravenously into a guinea pig of ordinary size, the only effects being a serous diarrhoea lasting for a few days, the result of the greatly increased amount of fluid in the animal's body. Hamburger (1908) emphasized the harmlessness of tuberculin to nontuberculous persons, stating that Old Tuberculin had absolutely no recognizable toxic action on the "virgin" human organism. In contradistinction to this inertness in the nontuberculous, the results of an inoculation of tuberculin, even in minute quantities, are entirely different if given to an animal which harbors tubercles in its body. The animal reacts to the injection violently and characteristically, and, if the dose is sufficiently large, death results in a few hours.

The following experiment was carried out in order to find whether the urinary antigens act like true toxins or like tuberculin: A strong solution of mixed urinary antigen of ten far advanced active patients was prepared in such a way that 10 cc. of the solution contained the quantity of antigen excreted in 2000 cc. of urine by the patients. The antigen had been dialyzed for 24 hours in 80 per cent collodion tubes, but still contained the urinary pigments and the complex alcohol-insoluble nitrogenous products of Salkowski. No attempts were made to free the antigen from the latter substances, because experiments had proved that even thorough alcoholic-extraction methods were not sufficient to remove the tuberculous antigens from the alcohol-insoluble residue, and it was desirable to have as much antigen as possible for injection in this experiment. A solution similar to the above was also prepared from normal urines.

Six guinea pigs that had received intracutaneously the same dose of virulent *Mycobacterium tuberculosis* four weeks previously were the tuberculous subjects used. Each of these animals showed progressive

ulceration at the site of their original injection. Autopsies of animals that had received the same doses, but were not to be used in this experiment, indicated in the inoculated guinea pigs a general tuberculous adenitis, and also a few scattered tubercles in the spleen or liver, or in both of these organs. Three of the tuberculous and two normal

TABLE 6

Group I	Tuberculous guinea pigs that received intraperitoneal injections of 2 cc. of concentrated and partly purified tuberculous urines	All of the animals of this group became very sick within 10 minutes and had a tendency to fall on their side. One animal remained prostrated for 20 minutes, but no convulsive movements were observed. The animals of this group showed a temperature fall of 2°C. within 30 minutes. All animals returned to the condition in which they were before injection and lived from 8 to 14 days after the injection of the antigen
Group II	Normal guinea pigs that received intraperitoneal injections of 2 cc. of concentrated and purified tuberculous urines	For several minutes these animals appeared slightly indisposed. They would not attempt to run when approached. However, none of them had the tendency to fall on their side as those of group I. There was a slight increase in temperature. All quickly returned to normal
Group III	Tuberculous animals that received intraperitoneal injections of 2 cc. of concentrated and purified normal urines	Symptoms same as those in animals of group IV, though a little more pronounced. Animals died from 7 to 16 days after injections as the result of the infection
Group IV	Normal guinea pigs that received 2 cc. injections of concentrated and purified normal urines intraperitoneally	Slight indisposition for several minutes to move, but the animals soon became active again and appeared to have suffered no ill effects from the injections

guinea pigs were inoculated intraperitoneally with 2 cc. of the above-mentioned solution of concentrated and partly purified tuberculous urinary antigen, while the other three tuberculous and two normal anmals received 2 cc. doses of concentrated normal urines prepared in the same manner as the tuberculous urines.

Table 6 will show the results of the injections into the different groups of animals.

It is very difficult to give an accurate estimate on the amount of tuberculous antigen that was injected into animals of group II. However, it seems beyond question that if the antigenic substance were of either an endotoxic or exotoxic nature, sufficient antigen was introduced into the peritoneal cavities of the normal guinea pigs to produce more decidedly pathological symptoms than those that actually resulted. No appreciable difference in the effects of the tuberculous and normal urines could be observed in the normal animals.

On the contrary, in group I, of which the tuberculous animals received the products of the tuberculous urines, a very different result was observed from that in the animals of group III. The products of the normal urines did not cause the tuberculous animals to fall on their sides, as did the products of the tuberculous urines. It appears probably that if more of the active principle of the tuberculous urines could be injected into the tuberculous animals acute anaphylactic symptoms and death might result.

No effects from the intraperitoneal injection of the products of the tuberculous urines could be observed at the ulcerating foci of the tuberculous animals, but, nevertheless, the evidence from table 6 suggests that the antigens from tuberculous urines resemble tuberculin more than they do toxins as commonly understood.

Two other experiments were carried out to determine whether any definite biological, chemical, or physical relation could be established between the urinary antigens and Old Tuberculin. It has been reported frequently that individuals who reacted negatively to the first intracutaneous or ophthalmic test would react positively to a second injection in the same area. With this knowledge as a basis, attempts were made to sensitize the skins of three guinea pigs free from tuberculous infection, by intracutaneous injections of 0.1 cc. of 1/1000 dilution of Old Tuberculin and a similar amount of the urinary antigen from a strongly active case of tuberculosis. The areas which received the Old Tuberculin were tested against injections of both Old Tuberculin and the urinary antigen at the end of the fifth, tenth, and twentieth-day periods. No indications of a hypersensitization by any of the injections could be observed. The results in the areas that received the primary injections of the urinary antigens were also of an entirely negative nature.

Experiments to determine the relative diffusibility of the urinary antigens and Old Tuberculin were made, using the 80, 85, and 90 per

cent collodion sacs. The dilution of Old Tuberculin subjected to dialysis for 24 hours was 1/1000, as this amount approximated the quantity of tuberculous antigen in the urines used in these experiments. Five-hundredths cubic centimetre of the Old Tuberculin was injected intracutaneously in the forearm of an allergic individual, both before and after dialysis in the different sacs. The skin reactions resulting from these different injections indicated that none of the Old Tuberculin was lost by diffusion through any of the collodion tubes. This was quite different from the behavior of the urinary antigens, which were entirely lost through the 90 per cent sac and were slightly weakened by diffusion through the completely dried collodion tube that had been treated with 85 per cent alcohol. The 80 per cent sac possessed the most permeable membrane that prevented any loss by diffusion in 24 hours of the urinary antigens.

No diffusion experiments were carried out with the concentrated urinary salts where Old Tuberculin was in solution. It is quite possible that such a preparation of Old Tuberculin would show different properties of diffusibility from those reported above.

8. Practical application of the purification method

The following modification of the Wildbolz test has been applied, up to the present time, to 30 patients with definite clinical tuberculosis and 16 healthy persons. One hundred and fifty cubic centimetres of fresh morning urine were collected in flask A (fig. 1) and concentrated *in vacuo* to 1/10 the original volume. The concentrated residue was cooled thoroughly in the icebox for about an hour, then filtered through paper. The residue on the filter was washed with distilled water until the filtrate and washings totalled 15 cc. This filtrate was then dialyzed in running water for 24 hours through a completely dried collodion tube that had been treated with 80 per cent alcohol. The dialyzing residue was concentrated to dryness *in vacuo* and taken up in 15 cc. NaCl (0.85 per cent) solution. Five-hundredths cubic centimetre of this preparation of antigen was injected intracutaneously into an individual capable of responding to a 1/10,000 dilution of Old Tuberculin.

Tuberculous antigen was demonstrated by this method in the urines from 28 of the patients having definite clinical tuberculosis. The urines from the other two tuberculous cases were negative, but on a second trial within a week both reacted positively.

The greatest advantage of the modified method was seen in the work on the 16 normal urines. The nonspecific reaction that had resulted when Wildbolz's technique was used did not occur after the injection of the dialyzed urine. There was no greater reaction resulting from the latter than from the same quantity of NaCl (0.85 per cent) solution.

The injection of the urine as advocated by Wildbolz always caused a slight local burning pain for a few minutes. This undesirable factor was entirely eliminated by the purification of the inoculum.

This modification of Wildbolz's test has not been applied to any early cases of tuberculosis. It is in the diagnosis of this class of patients that a valuable laboratory aid is needed. Bosch has reported that the reaction is particularly strong in such a group of cases, but whether such a statement is true, when the purification method is used, it is yet impossible to say.

III. DISCUSSION

The questions, "Are there specific tuberculous antigens in the urines of active tuberculous cases?" and "What is the nature of these antigens?" are more fundamentally important than the practical value of the Wildbolz auto-urine test. The earlier idea that in the patient harboring active tuberculosis the *Mycobacterium tuberculosis* secreted a toxin which was responsible for the pathological changes and clinical symptoms is not acceptable in the light of our present knowledge. How Maragliano was able to cause toxic symptoms and death in normal animals by the injection of specific tuberculous toxin excreted in the urine of tuberculous patients and protect animals by injection of a specific tuberculous antitoxic serum cannot be understood to-day. There is some feeling on the part of the investigators of immunity in tuberculosis that not even endotoxins play a part in the pathology of the disease. They attribute the long chain of clinical symptoms to nonspecific toxic disintegration products of the tissues; as Krause (1916) has noted, the symptoms are due to "the absorption of focal products which react in an individual who is already sensitized to them rather than that they are the effects of any primary toxins that are elaborated in the focus."

It seems reasonable to believe that among these focal products there are one or more chemical substances derived from or related to the

Mycobacterium tuberculosis. Hypersensitiveness to products of the etiological agent is manifested in the great majority of individuals infected with *Mycobacterium tuberculosis*. This fact suggests the idea that a specific sensitizing product is absorbed from the focus and circulates throughout the body, causing the changed reactivity of the tissues known as *allergy*. This specific sensitizer is quite generally spoken of as a tuberculin, although experiments to prove this point are scanty. Baldwin (1910) noted that "auto-sensitization is not a sensitization to any product with which we are familiar. It may be a complex product formed by the interaction of the bacilli and tissue cells of the focus." Paterson (1918) termed the sensitizer "the active principle" and many others use the term "tuberculo-protein."

Many serious technical difficulties exist in any attempt to acquire more definite information about such a specific sensitizing product. It seems as if the best method of approach to the problem would be the demonstration of such a substance in the urine of tuberculous patients. From the knowledge derived from other diseases it is plausible to suppose that antigens of *Mycobacterium tuberculosis* are present in the urines of patients with active tuberculous disease.

If it is granted that specific metabolic products of *Mycobacterium tuberculosis* or split products due to digestion by tissue enzymes are present in the urine, then the question arises, "How are they to be demonstrated?" It is certain that the evidence obtained by intracutaneous skin tests, as practised by Wildbolz, is not sufficient. The results of these tests will always be questioned, as long as so much nonspecific material as is present in the concentrated urines is injected intracutaneously. Though the method of purification advocated in this report is of value in eliminating nonspecific reactions, the intracutaneous skin test is such a delicate means of obtaining a nonspecific inflammation, as well as the definite local allergic response, that some other method of a confirmatory nature is necessary.

The skin test might also be criticized unfavorably because it has been proved that in cases of syphilis, typhoid fever, and glanders an allergic response can be obtained by luetin, typhoidin, and mallein respectively. Although Wildbolz obtained negative results in many kinds of infections, including syphilis and typhoid fever, it is not easily conceivable why patients with other infectious diseases do not excrete in their urine antigens which would cause positive auto-urine reactions.

The work of Ichok, if confirmed, would be very valuable in ascertaining the presence of a specific tuberculous antigen in the urines of tuberculous patients. He injected 2 cc. quantities of the concentrated urines from tuberculous patients who had no renal involvement, at five-day intervals, into three rabbits. After eight months he was able to detect tuberculous amboceptor by complement fixation, using Besredka's antigen.

The method used by Čepulič offers an important link in the chain of evidence that a tuberculin-like substance is excreted in the urines of certain tuberculous patients. Čepulič injected subcutaneously the concentrated and filtered urine of an active tuberculous patient into a tuberculous individual. Twenty-four hours after the injection the patient exhibited great uneasiness, headache, great exhaustion, focal reaction recognized through the increased physical signs, increased râles, coughing and slight hemoptysis existing two days. The intracutaneous reaction in another allergic individual with the same concentrated urine gave a 1/1000 reaction compared with the Old Tuberculin control. Control injections with the same and still greater amounts of a normal concentrated urine which reacted negatively on intracutaneous injection caused no focal reaction.

In this work a urinary antigen, after concentration and purification, was detected by complement-fixation technique, using several known sera containing tuberculous amboceptor; and intraperitoneal injection into tuberculous guinea pigs of urinary antigens caused results which are definitely specific as compared to the controls.

As to the nature of the urinary antigens, the evidence advanced up to this time tends to exclude protein. The physical nature as evidenced by diffusion experiments shows that the antigen is made of molecules smaller than ordinary protein molecules. No work that has come to the writers' attention has demonstrated that the antigen reacts positively to the common protein tests. In this investigation an antigen of lipoidal nature was demonstrated, but it seems possible that in the light of present partigen studies more than one antigenic group might be present in the urines of the same or different tuberculous patients. It is probable that the fundamental chemical studies on *Mycobacterium tuberculosis* that are being reported by Long (1919) (1921) and Johnson and Brown (1922) will lead to a more exact study on the nature of urinary antigens.

Before the Wildbolz test becomes valuable as a practical aid in the diagnosis of tuberculosis, the reaction will have to be studied in a large number of incipient cases. Just what a positive Wildbolz reaction will mean is difficult to judge. It seems probable th t it will indicate pathological activity. But until physicians accept one valuable standard of clinical activity, in relation to which the Wildbolz reaction can be compared, there will always be doubt as to the exact value of the test.

CONCLUSIONS

1. The Wildbolz auto-urine test gives much promise of becoming a valuable laboratory aid in the diagnosis of clinical tuberculosis, if the nonspecific reacting elements of concentrated urines are removed.

2. The method of Brown for the preparation of collodion tubes of different permeabilities was found to be of much practical value.

3. Dialysis of the patient's urine, after concentration to 1/10 its original volume, in a collodion tube treated with 80 per cent (by volume) ethyl alcohol is a satisfactory method of obtaining a solution of partially purified antigen. Thorough extraction of the nondiffusible residue with absolute alcohol will yield a highly purified antigenic preparation, but it is not sufficient to obtain the entire quantity of antigen.

4. The tuberculous antigens in the urine of active tuberculous patients are entirely lost by a semipermeable membrane that allows diffusion of starch and serum albumin. They are weakened by dialysis in membranes that allow slow diffusion of erythro-dextrin, and held back by membranes that retain the dextrin.

5. No evidence could be obtained that any of the tuberculous antigens of urines were protein in nature. The alcohol-soluble antigenic fraction was of the nature of a phosphatid, possibly mixed with a slight trace of protein.

6. The antigen seems to be of a tuberculin nature, and is strongly resistant to various physical and chemical agents.

Addendum

Since this paper was written, Korns (AMERICAN REVIEW OF TUBERCULOSIS, 1923, vii, 318–324), Hayman (AMERICAN REVIEW OF TUBERCULOSIS, 1923, vii, 325–331), HENRICHSEN (AMERICAN REVIEW OF TUBERCULOSIS, 1923, viii, 341–357), and ORNSTEIN (AMERICAN REVIEW OF TUBERCULOSIS, 1923, viii, 366–370), have reported work on the Wildbolz reaction. Korns questioned the specificity of the test, due to certain theoretical considerations, while Ornstein presented experimental evidence which seemed to prove that there was no specific antigen present in the urines of active tuberculous patients. Hayman, on the contrary, reported that, "The test, while theoretically sound, is beset with so many sources of error in its present form that a reliance cannot be placed upon it equivalent to clinical criteria at present in use." He thinks that "a definitely positive reaction, properly controlled, is indicative of active tuberculosis and that a negative test is of less value unless repeated."

Ornstein used a fishskin sac for dialyzing out the urinary salts, and tuberculous guinea pigs for the skin reaction in testing for the presence of antigen. We are of the opinion that the discrepancy in his and our results might be due to a greater permeability in his dialyzing sac than in our 80 per cent alcohol-treated collodion sac (see tables 3 and 4), or to the fact that the allergy of the skins of his tuberculous guinea pigs was controlled with a 1 to 100 dilution of O. T. At best, there seem to be only minute quantiturof ies rainy antigen present in tuberculous urines. Therefore, an allergic skin that reacts to a 1 to 100 dilution and fails to react to a 1 to 1000 dilution of O. T. might readily be of too slight sensitiveness as a detector for the presence of urinary antigens.

Henrichsen and Sweany obtained encouraging results by the application of the auto-serum test to tuberculous and normal individuals, although certain diseases other than tuberculosis were found to elicit the reaction.

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HELIOTHERAPY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

HORACE LoGRASSO AND FRANK C. BALDERREY

Of the treatment of the many manifestations of tuberculosis that of the purely pulmonary type by heliotherapy is perhaps the most disputed. The good effect of solar radiations as a means of treating extrapulmonary tuberculosis has gradually been acknowledged, as a result of the work of Rollier in Switzerland and of the J. N. Adam Memorial Hospital in this country, but its value in pulmonary tuberculosis has not been established up to the present time.

Rollier has devoted a very limited amount of space to this subject in his book. He begins by saying

> To treat it adequately is beyond our power as our experience has been almost confined to surgical manifestations of the disease; properly applied I am convinced that heliotherapy would be a useful factor in the treatment of the great majority of cases of pulmonary tuberculosis. Heliotherapy has not yet won its spurs in the treatment of pulmonary tuberculosis; its results have, none the less, been sufficiently good to encourage our colleagues whose experiences in this disease are greater than our own to make a serious attempt to apply systematized sun treatment to suitable cases under their care.

One of the outstanding features in all previous reports of the use of heliotherapy in pulmonary tuberculosis is a lack of accuracy on the part of the various clinicians in describing their technique. There have apparently been none who used the systematized, gradual insolation as prescribed by Rollier. Judging from the available literature, the methods employed by different clinicians seem to vary considerably. Malgat, who in 1904 first used heliotherapy in the treatment of pulmonary tuberculosis, subjected his patients to radiations of but twenty minutes a day, exposing only the chest. He considered the sunbath cold if a thermometer registered a temperature below that of the body. Pottenger and Kime used, in addition to the general sunbath, reflected light upon the chest.

[1] From the J. N. Adam Memorial Hospital, Perrysburg, New York.

Bacmeister gave long periods of exposure on the chest alone. He, as well as Jacquerod, reported unfavorable results, and abolished its use in pulmonary tuberculosis. Others who have employed this form of treatment and who have, to a large extent, discontinued it are Liebe, Röpke, Schroeder and Bandelier.

The length of the radiation periods has varied from twenty minutes to six hours per day. In some instances cold baths, showers or sponge baths have been advised, following solar radiation. These variations in technique easily account for the differences in the results obtained, and the many contraindications to its use that have been brought forth. Many of the haphazard methods employed in giving suncure would not be recognized as heliotherapy, either by Rollier or by others who have had extensive experience.

There are numerous untoward symptoms which have been attributed to the use of light in pulmonary tuberculosis and which would contraindicate its application in this disease. Hemoptysis is one of the most disputed of these complications and is also the most serious. To lessen this possible danger it has been suggested that the chest be not exposed to the rays of the sun. Jacquerod, who has discontinued the use of heliotherapy in pulmonary tuberculosis, found this complication occurring. Bacmeister also encountered hemoptysis, and attributed its occurrence to the radiations. Pottenger, Holmboe and Morin take the opposite view, and hold that heliotherapy does not produce hemoptysis. Moreover, Morin observed that in those with previous histories of hemorrhage it did not recur with exposure to light. An increase in the activity of the lesion, or the reactivation of one which has been arrested, has been observed by Jacquerod and Bacmeister. Temperature and pulse rate have often been found to rise sharply. Headache, insomnia, palpitation, anemia, anorexia and hysteria have also been mentioned. It would appear more than probable that these complications are due to the faulty technique in using solar radiations; for, according to our experience, the occurrence of many of these might be produced by variations in the dosage and in the time of day selected for the application of solar energy.

Progressive pulmonary lesions with high fever and rapid pulse have been looked upon as contraindications. Insomnia, hyperthyroidism and obesity, particularly when present in patients with valvular heart disease, have been further additions to the list of contraindications.

For the past eleven years heliotherapy has been used at the J. N. Adam Memorial Hospital, Perrysburg, New York, as a routine method of treatment in all forms of tuberculosis except the purely pulmonary type of the adult and far advanced pulmonary tuberculosis in children. During these years we have noticed, in the treatment of patients with extrapulmonary lesions with marked pulmonary involvement, a tendency of the pulmonary disease to assume a mild course and to become quiescent in an unusually short time. Rollier, in his experience with extrapulmonary tuberculosis, reports good results in some of his patients who were in the second or third stage of pulmonary disease. He suggests that they may have developed an immunity with their surgical condition. For this reason we cannot form an opinion as to the response to treatment of pulmonary tuberculosis by comparisons drawn between the behavior of pulmonary disease existing alone and the behavior of such lesions coexisting with extrapulmonary foci. It would follow that any decision as to the advisability of using suncure in pulmonary tuberculosis would have to be based upon our experience with purely pulmonary cases.

We must confess that up to a few years ago we were rather skeptical as to the efficacy of heliotherapy in pulmonary disease, and we therefore discouraged its use. However, a certain number of our patients, noticing the rapid progress made by some of the extrapulmonary cases, used, against our advice, suncure as a part of their treatment. These patients could not carry out insolation systematically, first, because of a lack of proper facilities, and secondly, because of the absence of proper supervision. The staff of the hospital was for a time depleted to such an extent that proper supervision of these cases was impossible. The effects noted were interesting and gave valuable information as to the precautions which are necessary to make heliotherapy safe in pulmonary tuberculosis.

One of the first ill effects noted was the occurrence of an unusual number of hemoptyses. Other patients developed elevations of temperature up to 102°, lasting for two or three days at a time. Accompanying this fever were headache and nausea, usually present for 48 hours. It was discovered that these patients had been exposing themselves to the sun for extremely long periods, as long as 7 hours a day. Others had exposed only their chest to the sun, insolating it for practically the entire day. Hemoptysis did not seem to have developed more frequently in these cases that exposed only the chest the whole day than in those who ex-

posed the whole body for long periods. Barring the ill effects occasionally noted, we were compelled to admit improvement in the general physical condition and the local disease in the majority of cases. Encouraged by these improvements and being convinced that the ill effects were due to improper technique, we decided in the summer of 1922 to conduct a thorough clinical investigation of the use of light energy in pulmonary tuberculosis, in the hope of extending this form of therapy to all types of this disease. This work was continued during the summer of 1923.

We felt confident that with the observance of every possible precaution insolation could be made perfectly safe. The first step was to provide individual attention and supervision of these patients. This prevented overinsolation. Secondly, we changed the hours for insolation to early morning and late afternoon. In this manner we utilized solar energy at times when its intensity was less and obtained stimulating effects. For these patients the insolation period was limited to three hours per day, but they were encouraged to expose their bodies to the air throughout the day by remaining in the shade and wearing only the breech-cloth.

In 1922 and 1923, eighty-nine cases were selected for observation. Of this number 40 who were doing well were obliged to leave the hospital for various reasons before the completion of three months of heliotherapy. Our report is based upon the remaining 49 cases, who were under sun-treatment continuously from May to October. We felt that complete and careful observations on a few cases would be of more value in the end than a few clinical notations on a large number. In addition to these selected cases, about 40 more patients subjected themselves to solar radiations at the same time; but, since the majority of these were in the incipient stage and had been responding favorably to rest, they were not included in the series. In the main, our cases were chosen not because of their favorable prognosis but because they were not responding favorably to the usual intensive hygienic treatment. All of them had been in the hospital at least six months. Hemoptysis had been a frequent complication, four having had hemorrhage three weeks prior to the beginning of treatment. All had fever upon admission to the hospital and some at the beginning of their insolation were having elevations of temperature as high as 101°F. In short, they were, as a whole, cases with moderately advanced pulmonary tuberculosis, active, not tending to quiescence or arrest, and with unfavorable prognosis after thorough rest-cure.

We acquainted these patients with the many harmful results reported by observers in the employment of heliotherapy in pulmonary tuberculosis, but at the same time we expressed our confidence in the treatment provided we had their full coöperation. In spite of the element of uncertainty, the number wishing to take advantage of the treatment was so large that it was impossible to maintain rigid clinical notation on all who wished to avail themselves of the opportunity. Limited facilities precluded a large series, and in our selection of cases we gave preference to those patients who had proved conscientious and earnest and who would be amenable to the routine prescribed for them.

Before the beginning of treatment each patient was examined, and careful observations were made as to the extent and activity of the lesion, general physical condition, the character and amount of cough, ease with which the sputum was raised, temperature, pulse, respirations, blood pressure and weight. The sputa were examined, and counts made of the number of tubercle bacilli or other bacteria per high-power field. Urinalysis was done. A complete blood examination, including differential count, was made. Photographs were made and radiographs of the lungs obtained. With the exception of the photographs and radiographs, which were taken before and after treatment, the above data were obtained each month during the term of treatment. The amount of sputum expectorated during the twenty-four hours was weighed daily. As any change or untoward symptom occurred, it was reported either by the nurse or patient, and its occurrence included in the data.

The solar radiations were given on the roofs of the solaria, which were well protected from winds. Exposures were taken either on cots or on blankets, the patients being fully exposed to the sun's energy except for a breech-cloth.

A modification of the Rollier technique of accustoming the patient to the sun's energy was employed, as in the cases with predominant extrapulmonary lesions. Great care was exercised in this, as many of the cases had had previous hemorrhage and some few had had hemoptysis and fever no longer than three weeks prior to their first radiation. The technique was as follows:

First Day: The patient, reclining on a bed, and with eyes protected from the sun by means of colored glasses or towel and the head by a linen cap or bonnet, was taken to the sunporch. The only clothing worn were trunks. Only the feet were exposed and irradiated on this day. They were insolated for periods of five minutes three times during the day with intervals of about one hour.

Second Day: Each insolation period of the feet was increased to ten minutes, and more of the body was treated by insolating the lower extremity from the knees to the ankles for five minutes.

Third Day: The feet were irradiated for fifteen minutes at each period. The time of insolation, from the knees to the ankles, was increased five minutes, and still more of the lower extremity treated to insolation by exposing from the hips to the knees for five minutes.

Fourth Day: The entire lower extremity was now receiving sunlight in the following doses: hips to knees, 10 minutes; knees to ankles, 15 minutes; and feet 20 minutes. The abdomen was now insolated for five minutes.

Fifth Day: The insolation periods were now: abdomen, 10 minutes; thighs, 15 minutes; legs, 20 minutes; and feet 25 minutes. The last part of the body to receive its initial insolation, the chest, was now exposed for five minutes.

FIG. 1. CHILDREN TAKING THE SUN-CURE.

The periods of insolation were correspondingly increased 5 minutes each day upon each previous subdivision of the body, until on the 12th day the longest-exposed part received a total radiation time of three hours, the exposure periods being: for the feet, 60 minutes; knees to ankles, 55 minutes; thighs, 50 minutes; abdomen, 45 minutes; and chest, 40 minutes. From this day to the 16th the insolation period of the feet remained 60 minutes. The remaining subdivisions were increased by 5 minutes each day until each subdivision received 60 minutes irradiation. On the 17th day the insolations were reduced to one morning and one afternoon period of 90 minutes each. The anterior and posterior surfaces received the same amount of radiation, the total exposure being divided equally between the two surfaces.

All cases were advised to take an air bath during the regular hours, when the sun's energy was not available for radiation. No more than three hours of sun per day, or one and a half hours for a single exposure, was allowed. This was found to be necessary, as the patients had a tendency to increase the radiation time in the hope that a cure might be more quickly effected.

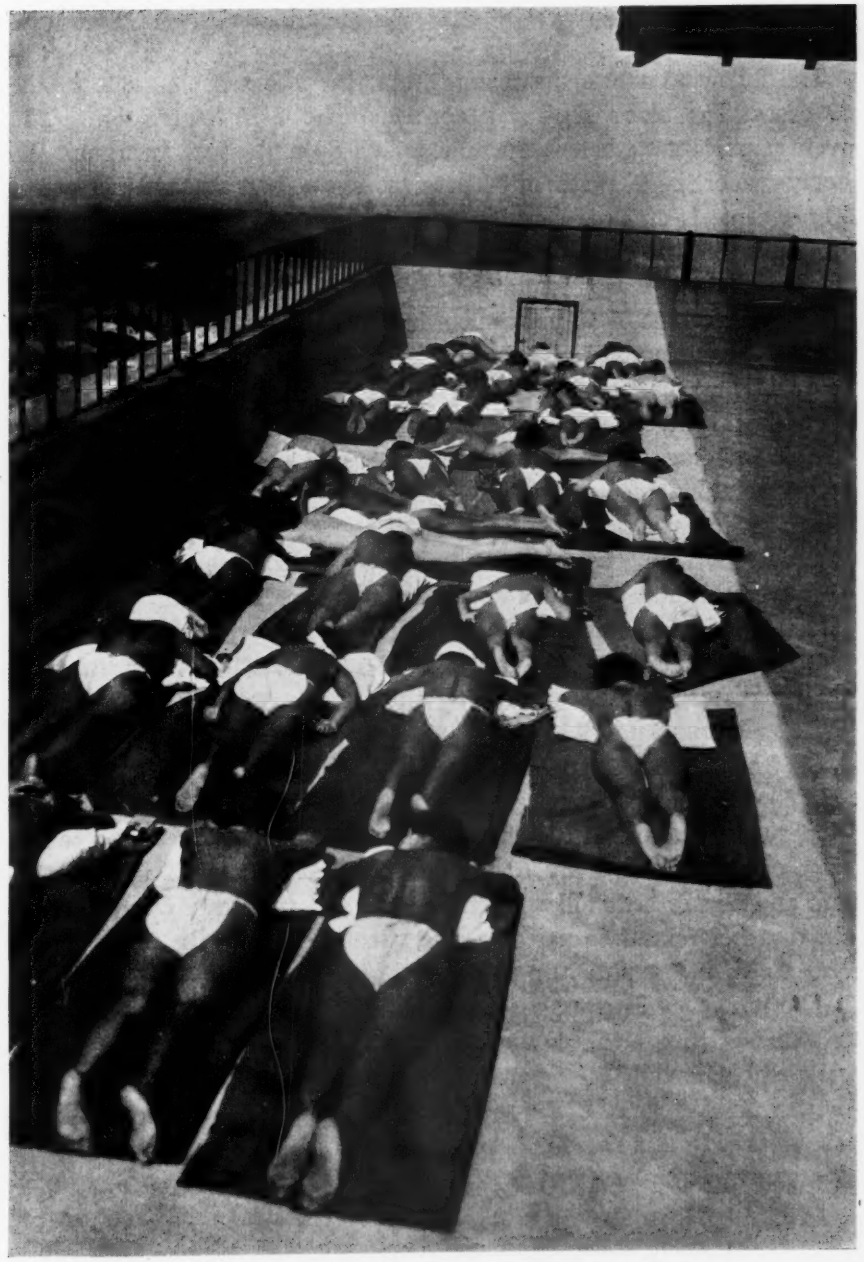

FIG. 2. SUN-CURE AS CONDUCTED IN PULMONARY CASES

The pulse, temperature, respiration and blood pressure were observed before, during and at the end of the radiation periods.

The following shows the results from the observations made in the 49 cases: The blood showed a decided increase in hemoglobin. The average percentage before treatment was 80 and after treatment 90. Forty-two of the 49 cases, or 86 per cent, showed an average increase of 10 per cent; 1, or 2 per cent, an average decrease of 5 per cent; and 6, or 12 per cent, no change. Studying the figures from the standpoint of stage of disease, it was found that 7, or 100 per cent, of the incipients gained an average of 15 per cent of hemoglobin; and that 33, or 89 per cent, of the moderately advanced showed an increase of 10 per cent, while 4, or 11 per cent, remained stationary. Of the far advanced cases, 2, or 40 per cent, showed an average increase of 5 per cent; 1, or 20 per cent, an average decrease of 5 per cent; and in 2, or 40 per cent, the hemoglobin remained unchanged.

In practically all of these cases the initial white-cell count showed a leucocytosis with the polymorphonuclear leucocytes predominating. The average total white-cell count of this series before treatment was 12,000. Before treatment incipient cases had an average count of 9,500, those with moderately advanced disease 12,400, and those with far advanced disease 14,500. Following their treatment the average total white cell count was 9,500. The incipients had an average count of 8,000, the moderately advanced 9,500 and the far advanced 11,000.

Differential counts showed the polymorphonuclear cells averaging 74 per cent before and 66 per cent after treatment. According to the stage of disease, the early cases showed an average of 72 per cent before and 62 per cent following treatment; the moderately advanced 74 per cent before and 66 per cent after treatment; and the far avanced 77 per cent before and 70 per cent following treatment.

The lymphocytes averaged 21 per cent before and 28 per cent after treatment. Six, or all of the incipient cases, showed an average of 24 per cent before and 31 per cent after treatment; the moderately advanced showed an average of 22 per cent before and 28 per cent afterward; the far advanced cases showed 18 per cent before and 25 per cent following treatment.

Forty-two, or 84 per cent, of the series were not having fever at the time of beginning suncure. Seven, or 16 per cent, of those with moderately advanced tuberculosis were running a temperature of over

99.2°F., at times 101°F., and of these, 6 returned to normal during two weeks' time of treatment and one during the fifth week.

The pulse rate did not show great response to the radiations. Twenty-one, or 42 per cent, had an average increase of 6 per minute; 10, or 20 per cent, an average decrease of 7 per minute; and 18, or 36 per cent, no change. Examinations of the sputum showed that, per high-power field, the tubercle bacilli were increased in 18, or 36 per cent; decreased in 20, or 40 per cent; and without change in 11, or 22 per cent. Of those with second-stage disease, 4, or 11 per cent, showed an increase; 26, or 70 per cent, a decrease; and 7, or 18 per cent, no change. The third-stage cases showed an increase in 3, or 60 per cent, and no change in 2, or 40 per cent. The sputum was persistently positive in 43, or 88 per cent, of this series before treatment; 19, or 44 per cent, of these positive cases became negative after treatment as shown by three consecutive examinations.

The total amount of sputum expectorated in 24 hours averaged, for these cases, 35 gm. at the beginning and 28 gm. at the end of treatment. The average daily amount expectorated increased in 11 per cent and decreased in 78 per cent.

The changes in weight were as follows: 28, or 56 per cent, showed an average gain of 4 pounds; 13, or 26 per cent, an average loss of 1 pound; and 8, or 16 per cent, remained stationary. All the incipient cases gained, the average gain being 3 pounds; of the moderately advanced, 21, or 57 per cent, showed an average gain of 5 pounds; 14 per cent showed no change; and 11, or 29 per cent, showed an average loss of 1 pound. Two, or 40 per cent, of the far advanced cases had an average gain of 4 pounds; 2, or 40 per cent, an average decrease of 1 pound; and 1, or 20 per cent, remained stationary.

The physical examinations gave the following results at the end of the treatment period: 38, or 77 per cent, improved; 3, or 6 per cent, showed more signs; and 8, or 16 per cent, showed no change. Of the incipient cases, 6, or 86 per cent, improved and 1, or 14 per cent, remained unchanged. Of the moderately advanced, 31, or 84 per cent, improved; 4, or 10 per cent, remained stationary; and 2, or 6 per cent, showed more signs. Of the far advanced, 1, or 20 per cent, improved; 1, or 20 per cent, showed more signs; and 3, or 60 per cent, remained stationary. From the general appearance all of these patients showed marked improvement.

When we consider that these patients were selected, first, because they had not responded to previous intensive hygienic treatment and, secondly, because they were progressing, we must acknowledge that the results were most satisfactory.

The radiographs in these cases did not show marked changes after three months of treatment.

TABLE 1

Results of treatment and nutritional changes

STAGE OF DISEASE	IMPROVED	NO CHANGE	PROGRESSIVE	WEIGHT				
				Gain	Loss	Stationary	Average gain	Average loss
							pounds	*pounds*
I	6 or 86%	1 or 14%		7 or 100%			3	
II	31 or 84%	4 or 10%	2 or 6%	21 or 57%	11 or 29%	5 or 14%	5	1
III	1 or 20%	3 or 60%	1 or 20%	2 or 40%	2 or 40%	1 or 20%	4	1
Total...	38 or 77%	8 or 16%	3 or 6%	28 or 56%	13 or 26%	8 or 16%	4	1

TABLE 2

Results of blood examinations

STAGE OF DISEASE	HEMOGLOBIN			TOTAL LEUCOCYTES			POLYMORPHONUCLEARS			LYMPHOCYTES		
	Average before	Average after	Average increase	Average before	Average after	Average decrease	Average before	Average after	Average decrease	Average before	Average after	Average increase
	per cent	*per cent*	*per cent*				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
I	80	95	15	9,500	8,000	1,500	72	62	10	24	31	7
II	80	90	10	12,400	9,500	2,900	74	66	8	22	28	6
III	80	85	5	14,500	11,000	3,500	77	70	7	18	25	7
Total.....	80	90	10	12,000	9,500	2,500	74	66	8	21	28	7

As in those with extrapulmonary lesions, the improvement in the patients' appearance was striking. The musculature became hard and firm. Improvement in the coloring of the mucous membranes was obvious. Their expression showed increasing good spirits and animation. The cure-hour was looked forward to as a pleasurable incident and not an irksome duty.

It has been said that the value of heliotherapy is dependent, to a great extent, on its psychic effect. Supposing this to be true, the mere chang-

ing of the patient's attitude toward the rigid regimen, which he must follow to obtain the arrest of his disease, is in itself a wonderful aid. If heliotherapy does this it is a therapeutic agent not to be despised.

From daily clinical observations of these cases much valuable information was obtained. Temperatures taken during the radiation periods did not show an increase of more than 1°F. There was a slight decrease in blood pressure during these hours. Before insolation the blood pressure averaged systolic 119, diastolic 75; and after it, systolic 113, diastolic 68. As noted above, there was a slight loss of weight in a few of the patients; but in no instance was this loss of serious importance, two pounds being the greatest decrease throughout several months of treatment. Moreover, these losses were in all probabliity due to the fact that the patients perspired freely while in the sun and that they had already reached a maximum weight. There were no hemorrhages, not even streaked sputum, in the 1922 group, in spite of the fact that 11, or 58 per cent, had had previous hemoptysis. In the 1923 group, however, we had one hemorrhage; but this was in the case of an overzealous patient, who, after the usual morning exposure, continued the cure on a sand-pile until noon, making a total irradiation period of three hours. This was the only case of hemoptysis in the series, and it must be attributed not to heliotherapy but to the injudicious use of light energy.

The usual information as to the sputum was that expectoration was more easy and that it occurred practically only during cure-hours. During the first six or eight weeks of suncure the expectoration increased from 10 to 20 gm., but after this there was a gradual decrease to either the original amount or less. The cough was lessened in every case, and in some cases it disappeared entirely.

The appetite in all the patients improved and constipation, when present, was relieved. The strength of the patients increased, and as they progressed it was at times difficult to restrain them from overexercise. In those patients complaining of dyspnea some improvement was apparent to the physician; and from the statements of the individuals there was no doubt in their minds that it was markedly better. All of those who were having night sweats at the beginning of treatment were free from them after the first month.

In the series we had one case complicated with rectal fistula, one with tuberculous laryngitis and one with pyopneumothorax. All of these complications were markedly improved. At this point we wish to note that during the last eleven years it has been customary in our institution

to treat all pneumothoraces and pleurisies with effusion, complicating tuberculosis, with heliotherapy. We have discharged, up to 1924, 47 cases of pulmonary tuberculosis complicated with pneumothorax and 92 complicated with pleurisy with effusion. The results in these cases may be called brilliant.

We are so encouraged by our experience with suncure in pneumothorax cases that we are contemplating using a combination of heliotherapy and lung-compression.

Heliotherapists have observed that, following the discontinuance of the insolation periods during the winter, the condition of the patient either remains stationary or retrogresses. Most of the interruptions are caused by the daily and seasonal changes in the weather characteristic of the climate in which solar therapy is practised. This has led to the substitution of artificial sources of light energy without thought as to their spectral characteristics or intensity. Others have formed theories as to the wave-lengths most effective in the cure of tuberculosis and, to substantiate these theories, have used artificial light sources rich in certain portions of the spectrum.

Up to the present the results of treatment by artificial light have been decidedly inferior to those from heliotherapy. The two main reasons for this are, first, that while heliotherapy is practised under ideal conditions, artificial light treatments are given in small, ill-ventilated rooms the air of which is vitiated and often filled with gases emitted from the lamps; and, second, up to the present, artificial light units have been deficient in intensity and limited as to their spectral distribution as compared with the sun.

Compared with summer sunlight the mercury arc in quartz is very deficient in visible and infrared radiation, though it produces an abundance of ultraviolet rays. Moreover, a considerable portion of the ultraviolets that it radiates are of shorter wave-length than any ultraviolets present in the solar spectrum. The ordinary carbon arc gives out a great deal of infrared and is deficient, compared with sunlight, in the visible portion of the spectrum, particularly in the blue-green, green, and yellow portions, but not to as great an extent as the mercury arc. Like the mercury arc it produces short wave-length ultraviolets not present in sunlight. The gas-filled tungsten incandescent lamp, while very convenient to use, gives very little ultraviolet light, not only because of absorption by the glass bulb, but also because of the relatively low temperature of the radiating filament. Compared with sunlight, it is also

deficient in visible light, more particularly in violet and blue, while it radiates an excess of infrared.

In view of the superior results obtained by sun treatment, an artificial light has been developed in our Research Laboratory by our physicist, Dr. Brian O'Brien, in an attempt to imitate summer sunlight.

Total and spectroradiometric measurements of the light from these new lamps have shown that, as it reaches a patient about 7 feet away, it is identical with clear summer sunlight to a very good degree of approximation in every characteristic, including the actual intensity or brilliance. With one double lamp unit the entire body of as many as ten patients can be treated simultaneously with this intensity of radiation.

An unpolarized beam of light or, more broadly, of radiation, such as ordinary sunlight, can be completely specified by two things; namely, the total energy of radiation in the beam and the spectral distribution of that energy. The total radiation and spectral distribution of energy in sunlight, as it reaches the earth, have been carefully measured at Perrysburg by Dr. O'Brien, as well as elsewhere by many other investigators, and are therefore known. The lamps were developed to meet these known factors.

Experimental treatments with these lamps have shown that a smooth tanning of the skin is obtained practically in every way like that produced by sunlight and in about the same length of time required by sunlight. Further, a patient is warmed by the light to the same extent as by summer sunlight, so that the doors and windows of the treatment-room can be left wide open in all but the coldest weather, thus more nearly simulating the conditions under which heliotherapy is given. The lamps may also be run out-of-doors, even in a wind or rain, if necessary. While running indoors, provision has been made to eliminate any possible contamination of the air of the room by gases given off from the lamps.

While these lamps are still in the experimental stage, we feel that in the near future, after refinements have been made, we can offer to the clinician who wishes to employ light therapy a light source with spectral distribution and total radiation closely approximating sunlight and usable under conditions practically the same as in suncure.

SUMMARY

In conclusion we wish to emphasize the following points:

1. Heliotherapy is of the greatest value in the treatment of pulmonary tuberculosis, one of the most marked benefits noted being the striking improvement in the general physical condition.

2. The blood picture is improved, as is evidenced by an increase in hemoglobin, a diminution in the leucocytosis and a corresponding increase in the lymphocytes.

3. It lessens the activity of the pulmonary lesion, as indicated by the subsidence of fever, reduction in pulse-rate, decrease in moisture, cessation of night sweats, decrease in amount of sputum and greater ease in expectoration.

4. It greatly favors the absorption of exudates as in pleurisy with effusion, hydropneumothorax and pyopneumothorax, in which complications after the acuteness has subsided heliotherapy has proved of inestimable value.

5. It is the treatment of choice in so called surgical tuberculosis or, better, extrapulmonary tuberculosis.

6. It changes the mental attitude of the patient, and facilitates his recovery by making his treatment a pleasure rather than a distasteful necessity. But, while we admit the psychic effect as a factor not to be ignored, we do not, like some observers, attribute to it the entire benefit of heliotherapy, but insist that one must also accept the physical response of the individual.

7. According to our experience heliotherapy will not provoke hemoptysis, increase the activity of a lesion, or reactivate it if judiciously employed.

8. Moderate elevations of temperature, not due to acute complications, do not preclude its use, but we recognize as contraindications tuberculosis in the very active stage, marked toxemia and the acute miliary form of the disease.

9. Irradiation periods during the summer should be as early in the morning and late in the afternoon as is possible, as at this time the sun's energy is less intense and the chances of complications are reduced to a minimum. On the other hand, during spring and fall, the hours at the middle of the day should be chosen, as they resemble most closely the early and late hours of a summer day.

10. Artificial light therapy as it has been employed, with sources deficient in portions of the solar spectrum and total radiation, and

under entirely different conditions from suncure, cannot compare with heliotherapy. At its best it is only a poor substitute for solar energy.

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HELIOTHERAPY IN TUBERCULOUS SPONDYLITIS[1,2]

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Since 1903 when Rollier opened his first clinic at Leysin, heliotherapy has received considerable attention in medical literature. As a therapeutic measure which has come into such general use in Switzerland, both in the prophylaxis and treatment of tuberculosis, it deserves favorable consideration. Although this paper presents nothing new on the subject iteration may help to emphasize the value of an old remedy, which is not sufficiently appreciated, and which, from my own observation, is not always properly applied. In the State of Colorado, with its clear air and maximum amount of bright sunshine, there is not a single heliotherapy hospital. The hospitals in the City of Denver have sun porches, but they are not used to any extent, and there seems to be that lack of interest and enthusiasm for heliotherapy on the part of orthopedic surgeons, pediatricians and tuberculosis specialists, that are so essential for its systematic and successful application. Although sun treatment can be carried out advantageously in any hospital without special construction and equipment, a heliotherapy hospital or ward built and equipped for that purpose is necessary to interest patients and physicians and to obtain the best results.

The treatment of tuberculous patients in large government institutions has been rather discouraging. This can be explained on the ground that the class of patients treated are not especially coöperative. This, however, is not the only reason. Large tuberculosis hospitals function under a handicap as far as therapeutic results are concerned, because the individual treatment of patients so necessary for the success of a sanatorium has to be sacrificed more or less in the administration of such institutions. While admitting that the goverment's institutional treatment of tuberculosis has not been a great success, home treatment has been less so. The great difficulty has been to keep patients interested and to have them carry out their cure correctly. The hygienic treatment

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of tuberculosis is effective if patients can be kept contented and held under medical supervision for a sufficiently long period. Heliotherapy is in accord with the established routine treatment of tuberculosis, as it also involves rest, out-of-door life and air-baths. In addition to sun-baths, it moreover supplies a therapeutic diversion and aids in holding the patient voluntarily under a well-regulated regimen, which in the end, leads to recovery. There was a time at the Fitzsimons General Hospital when the treatment of tuberculous spondylitis was unsatisfactory. Heliotherapy was not used, and plaster casts were applied with little effect. With the patient's consent, the Albee bone-graft operation was performed. Few submitted to surgery, and the hygienic, mechanical and rest treatment was a failure, because the necessary coöperation could not be obtained. Then a heliotherapy ward was opened, the Rollier method of curing Pott's disease was introduced, and from that time on the difficult problem of effectively treating this class of patients has ceased to exist. Upon admission to the hospital, cases of spondylitis have the proper treatment explained to them, and are told that it will be necessary to rest in bed for two years and remain in the hospital for about three years. This comes as a disagreeable surprise, but when they realize that with time and care their disease is curable, and that there is only one alternative, namely, improper treatment with relapses, grave deformities and death, they almost invariably consent. After being transferred to the Heliotherapy Ward, and started in on their regimen amid patients who are cheerful and hopeful and progressing toward recovery, we have very little trouble in holding them. Heliotherapy patients improve so markedly in general health and appearance that it is no wonder that they become enthusiastic over the sun treatment and coöperate so closely with their physician.

The treatment of tuberculous spondylitis, as employed by us, is copied after Rollier's methods. The patient is kept in the recumbent position, absolutely flat on his back, with only a single pillow under the head. A bed without springs and a firm mattress are used, and equipped with rubber wheels, so that it can be moved about readily. The patient is then fitted with a plaster-of-Paris trough, somewhat arched so as to keep the spine in a position of lordosis. Very often this has to be accomplished gradually by means of pads in the bottom of the trough. In lower dorsal and lumbar Pott's disease, the trough is rather short, but if the cervical or upper dorsal region is involved, the trough extends the whole length of the spine. When the patient is taking a sun-bath

or is eating his meals, writing or working, he may assume an elbow-ventral posture, thereby keeping the spine in a position of lordosis. Only these two positions are allowed. When sunning in the dorsal position the trough is removed, and the patient lies with pads under the area of spinal involvement. He is kept out-of-doors day and night. The sun-baths are applied gradually, beginning with the feet, and increasing the time of exposure and part exposed daily, until the whole body is sunned. As a routine, the time of exposure is increased ten minutes a day; the feet are exposed the first day, the legs the second, the thighs the third, and so on with the abdomen, chest, neck and face, until the entire body except the head is radiated. This may have to be varied somewhat for individual patients and, likewise, the maximum time of exposure, which on the average is two hours in summer and three in winter. In summer, treatments are taken in the morning to avoid the depressing midday heat. When it is warm enough, the patient continues air-baths throughout the day. During the months of November, December and January, it is usually necessary to supplement sun-baths with Alpine-lamp treatments, using the sun for local exposure, and the artificial light for general radiation. Although a day or two of heliotherapy may be omitted occasionally, when there are long stretches of stormy and cold weather, other forms of light treatment should be employed. Patients, pigmented and hardened by exposure, can stand considerable cold, and, providing they are protected from the wind, may take general sun-baths even in midwinter. Wind-shields are improvised by means of various types of bed screens. As a rule, when patients first begin treatment for tuberculous spondylitis, they are kept in their troughs and in the dorsal position continuously, until all symptoms disappear and the acuteness of the disease subsides; then they are permitted to change to the elbow-ventral posture. In such instances, only the front of the body is sunned, sacrificing heliotherapy somewhat for absolute rest, when it is indicated. Cases complicated with active lung lesions are not permitted to expose their chests until the pulmonary tuberculosis becomes quiescent and then only for short intervals, increased very cautiously. No extension is applied to the spine unless there is an involvement of the cercival vertebrae, in which case it is obtained by means of a Thomas collar, or a jury-mast and weight and pulley traction. Postural treatment is usually continued for two years or longer, depending on symptoms or when the X-rays show clearing, fusion and fixation of the vertebrae. Before being allowed up, a celluloid

jacket reinforced with metal staves is fitted and the patient remains in the hospital six months longer, taking heliotherapy and graduated exercise. He is advised to wear his jacket for a year.

Serial roentgenograms are our best guide to treatment, and for this reason good clear-cut plates must be insisted upon.

Psoas abscesses, if accessible, are aspirated and injected with 10 per cent iodoform emulsion. Aspirations are made often enough to keep the abscess emptied, and the iodoform emulsion is injected in increasing amounts, beginning with 5 cc. and increasing 2 cc. a day to the point of tolerance. The aspirating needle is inserted in a different area each time through a sufficient thickness of healthy tissue, and, if practicable, from above, so that there will be no gravity seepage of pus through the necessarily large puncture wound. These precautions are taken to prevent sinus formation, and for this reason the part should be exposed to the sun immediately following the operation. Mixed infection sinuses are irrigated with 1 to 1000 mercurochrome or gentian-violet solution or injected with stronger solutions of the dyes or iodoform emulsion. The great difficulty of sterilizing the labrynth of tracts and pockets resulting from the psoas abscess makes the prognosis in such cases very grave. We have, nevertheless, improved most of these cases, and in one have succeeded in healing the sinuses completely.

Patients are not encouraged to undergo any of the ankylosing operations except occasionally, when for various reasons, such as psychoses, temperament, etc., they will not carry out the conservative treatment properly. Our motive for adopting this policy is on the ground that tuberculosis, no matter how it manifests itself, is a general disease and requires general treatment. Although a patient may be told that such an operation cannot replace the hygienic and mechanical treatment, and that its purpose is an attempt to hasten results, after the operation he is only too prone to neglect the latter, to lose interest, and to cease to coöperate fully. It is conceivable that in civil practice very often an attempt at a quick cure or a return to wage-earning as soon as possible is demanded, even though in the majority of cases this means faulty treatment, and is less economical in the long run. With government patients, however, this is not necessary, and we can use more time in an endeavor to obtain sure and permanent results. Fixation operations for tuberculous spondylitis may be compared to artificial-pneumothorax therapy in pulmonary tuberculosis, for the basic general treatment is still necessary in order to restore the failing immunity. In all forms

of tuberculosis, healing takes place by degrees, and, regardless of the therapeutic procedure, new foci can develop, complications arise, and relapses occur, which makes hygienic treatment and close supervision over a prolonged period advisable. To perform an operation with the idea of a quick cure makes it likely that one no longer has a coöperative patient. Such has been our experience. With children the duration of treatment is less a factor. They are perfectly contented and happy during rest-cures, especially when a number of them are together. Their schooling continues, and with prolonged hospitalization they do not become restless and introspective as do adults. However, the plan just described permits patients to do art and craft work, play games, learn typewriting, and pursue certain lines of study, so that they can be kept fairly well occupied and time made to pass pleasantly and rapidly. To interest the patients in their treatment, their exact condition is explained to them, and, throughout treatment, they are kept informed as to their progress. X-ray plates are shown, and any questions asked are honestly answered. When definite ankylosis or muscular atrophy occurs physiotherapy is employed.

Many cases of tuberculous spondylitis have pulmonary tuberculosis as a complication. Enforced rest for several years makes the spinal involvement a blessing in disguise.

Although not within the scope of this paper, it might be well to mention here that the sun treatment gives exceptionally good results in tuberculosis of any bone or joint, in tuberculosis of the lymph nodes, in genito-urinary tuberculosis, and in tuberculous peritonitis.

The question arises of how heliotherapy promotes healing in Pott's disease. While there is still considerable confusion in the efforts of scientific research to explain the physical, clinical and biological effects of heliotherapy, we know that remarkable results are obtained from this method of treatment, and the scientific reason is therefore of secondary importance. This much has been fairly well proved, namely, that the sun's rays in therapeutic doses have a bactericidal or a weakening effect on bacteria, that they stimulate normal tissues to increased exudation and more active proliferation and fibrosis around the tuberculous focus, that they destroy the pathological tissue of the focus, and have a decided analgesic effect. In addition to this, a beneficial general action, increased metabolism, improved skin function, and restoration of immunity can also be claimed.

In the study of our cases we have been impressed with the remarkable enthusiasm and coöperation shown by patients undergoing heliotherapy. Among the conspicuous outstanding results are healing phenomena, especially of the more superficial sinuses, analgesic effect, absorption of cold abscesses, healthy skin condition, and strongly developed musculature. Besides pigmenting, the skin becomes soft and velvety. The hairs on the surface of the body grow long and the sweat and sebaceous glands function more actively. Although confined to bed for a year or more, the muscular development of the patients remains excellent, and they are able to walk almost at once when permitted to be up. Rollier calls attention to the increased development of the back muscles under sun therapy, which acts as a splint to the spine.

Forty-five cases of tuberculous spondylitis have been admitted to our hospital since the Heliotherapy Ward was established in April, 1922.

Results of treatment show 6 cases apparently cured, that is, patients discharged or about to be discharged from the hospital; 6 arrested, meaning by this freedom from symptoms, spinal caries cleared, vertebrae ankylosed, and the patient allowed up in a jacket; 28 improved, 11 of these showing, besides symptomatic betterment, also X-ray improvement; 3 unimproved, of which one only took heliotherapy for a few days and left the hospital against medical advice, one was a case of dementia praecox, and the third a colored patient, who has mixed-infection fistulas and will not do what he is told. Two have died, one of gummata of the brain and the other of pulmonary haemorrhage. Eight cases were admitted with multiple mixed-infection fistulas. All but two have shown decided symptomatic improvement, and one has succeeded in closing and healing his fistulas, although very ill at the beginning. All except two are in good general condition, without any indications of nephritis or amyloid disease, and their ultimate recovery is hoped for. Eighteen patients had psoas abscesses on admission. This does not include the paraspinal abscesses seen in the roentgenograms, which are quite common. Eight had their abscesses aspirated and injected with iodoform emulsion; of these, 3 are apparently cured, 2 arrested, and 3 decidedly improved. In 14 cases, the tuberculous spondylitis occurred as a complication to pulmonary tuberculosis; in 8 the pulmonary involvement became arrested; in 5, improved; and in one the patient died of pulmonary haemorrhage. In 5 cases, an Albee operation was performed. Of these, one patient became worse after the operation, developing psoas abscesses and suppurating sinuses, and coöperating very poorly in his treatment; 3 cases

improved; and one became arrested. Twelve cases had spinal deformities; in one the kyphosis increased; in one it decreased; and in the others it remained the same. In 3 cases bony bridging between vertebrae occurred with healing. In 3 cases there were secondary foci in the spine. Two were complicated with genitourinary tuberculosis.

CONCLUSIONS

From our experience in treating tuberculous spondylitis, I believe that we are justified in drawing the following conclusions:

1. The conservative hygienic, postural, and heliotherapy method gives excellent results.

2. An ankylosing operation is only to be considered as an incident in the treatment, in no way modifying the conservative policy.

3. Psoas abscesses do not necessarily impair the prognosis unless permitted to rupture and become infected.

4. Cases with psoas abscesses, which are aspirated under aseptic conditions, seem to do surprisingly well.

5. Cases of Pott's disease, not correctly treated, usually develop deformities and multiple mixed-infection fistulas, with a grave prognosis, while those placed under a proper regimen do not have these complications, and they almost invariably recover.

6. Aside from its pronounced therapeutic effects, heliotherapy more than any other one procedure gains the coöperation of the patient, and carries him successfully through a tedious and prolonged treatment back to health.

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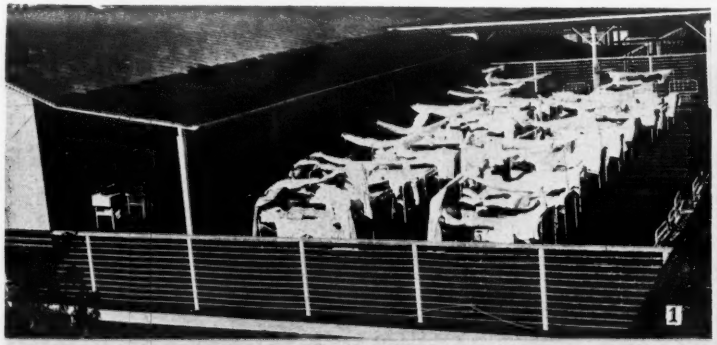


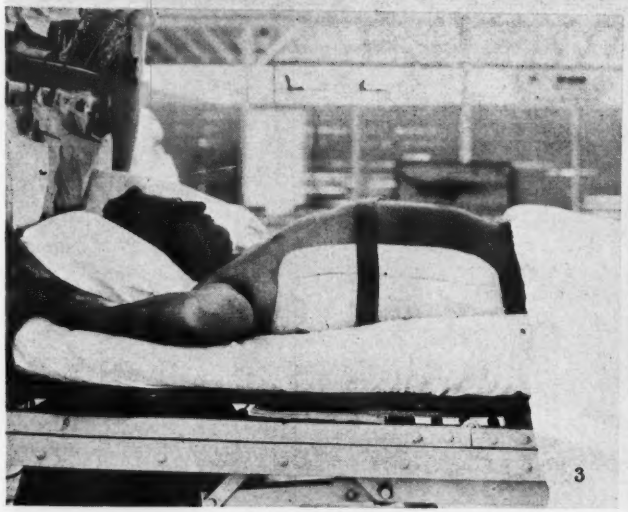
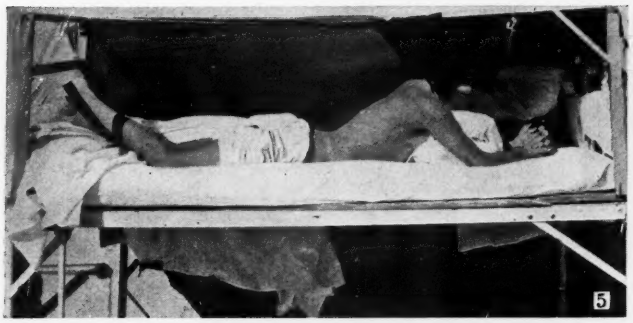


FIG. 1. SOUTH PORCH, HELIOTHERAPY WARD, FITZSIMONS GENERAL HOSPITAL, DENVER, COLORADO
FIG. 2. PATIENTS TAKING SUN-BATHS, HELIOTHERAPY WARD, FITZSIMONS GENERAL HOSPITAL
FIG. 3. DORSAL POSITION IN TREATMENT OF TUBERCULOUS SPONDYLITIS. PATIENT LYING IN PLASTER-OF-PARIS TROUGH
FIG. 4. DORSAL POSITION IN TREATMENT OF TUBERCULOUS SPONDYLITIS, SHOWING PADS UNDER SPINE



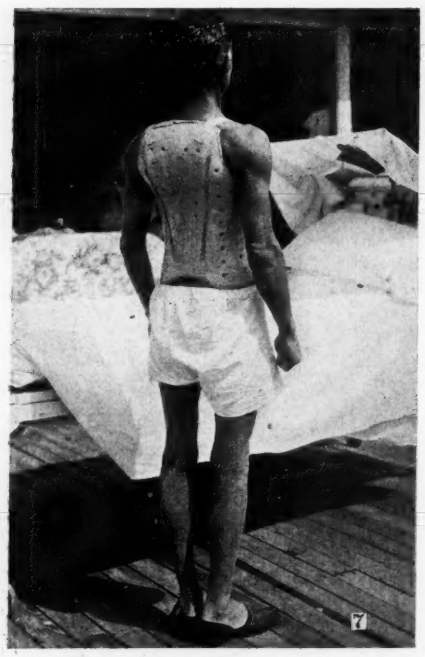


FIG. 5. ELBOW-VENTRAL POSITION IN TREATMENT OF TUBERCULOUS SPONDYLITIS; WIND-SHIELD ATTACHED TO BED

FIG. 6. CELLULOID JACKET USED IN TREATMENT OF TUBERCULOUS SPONDYLITIS (ANTERIOR VIEW)

FIG. 7. CELLULOID JACKET USED IN TREATMENT OF TUBERCULOUS SPONDYLITIS (POSTERIOR VIEW)

FIG. 8. PLASTER-OF-PARIS TROUGH USED IN TREATMENT OF TUBERCULOUS SPONDYLITIS

THE NON-EFFECT OF IRRADIATION WITH THE MERCURY ARC ON THE PRODUCTION OF AGGLUTININS FOR TUBERCLE BACILLI[1]

OTAKAR BARKUS

An increased agglutinin titre under the influence of heat has been observed by Lissauer (1), Fukuhara (2), and Lüdke (3); a rise of 1° to 2° in the body temperature produced the desired effect in rabbits immunized with typhoid and dysentery bacilli. Such a rise in body temperature occurs frequently during exposure to sun or artificial light, as has been shown in a previous report (4). Irradiation with visible light also produces hyperemia of the peripheral vessels, a factor which might well influence the formation of agglutinins. That repeated hemorrhage and other stimulation of the blood-forming organs causes increased agglutinin production has been proved by Hahn and Langer (5), Friedberger and Dorner (6), Roux and Vaillard (7), and Lüdke and Korper (8). Finally, there is Hansen's (9) recent work on typhoid agglutination in man during and after exposure to the carbon arc (75 amp., 55 volts, 1 m. distance) two and a half hours daily. He reports a "plateau" in the agglutinin curve, which in the untreated cases shows a rapid decline. Hansen intends to extend his work on the influence of irradiation to agglutinin-formation in tuberculosis.

The original plan for this investigation, which was started in February, 1923, was to study the formation of agglutinins, by means of a macro-agglutination reaction in tuberculosis patients exposed to sun and artificial light. Tubercle bacilli, bovine and human strains mixed in equal parts, were washed free from glycerol and suspended in double saline solution. This suspension gave constant titres with only a few tuberculous sera. Then Dr. Cori of the State Institute in Buffalo was kind enough to present to the writer an antigen prepared by Dr. W. Fornet; this antigen is a slightly turbid fluid and contains, according to Fornet's description, bacilli that have been treated for several hours with ether vapor at 40°C.; the fat of the microörganism is, however, not removed by ex-

[1] From the Department of Research, J. N. Adam Memorial Hospital, Perrysburg, New York.

traction but remains in the broth. This antigen, dried and stained, presents partly acid-fast, morphologically intact bacilli; it is produced by the *Laboratorium für Mikrobiologie*, Saarbrücken, Germany, on a commercial basis and the preparation of it is kept secret. The few results obtained during the first period of this experiment were very indefinite; however, after the sample of Fornet's antigen had been used, a similar antigen was prepared in this laboratory. Several methods, such as grinding of the bacilli and their suspension in double saline solution, ether extraction and suspension of the "defatted" bacilli, grinding and subsequent ether extraction, were tried and the following method, giving the highest titre, was finally adopted:

A mixture of human and bovine bacilli was washed free from glycerol, then washed by shaking and centrifugalization with cold absolute alcohol; this was followed by Soxhlet extraction with pure ether until the ether removed from the siphon tube, when evaporated, left no trace of fat; the bacillary residue was transferred to a flask containing 1.5 normal saline solution adjusted to pH 7.6 with sodium hydroxide; 1 cc. of toluene was added and the flask kept in the icechest.

The residue, fixed and stained with carbol-fuchsin and methylene blue, showed some acid-fast and some blue rods, morphologically unchanged; that is, some were granulated and some intact, just as in the original culture. This bacillary suspension is stable, only a small part settling out; the sediment formed was not disturbed and only the supernatant suspension was used in all experiments.

Eleven rabbits, 3 to 4 kg. in weight, were immunized with this antigen by a single intraperitoneal injection of 20 cc.; the serum obtained from the ear vein was titrated during the following days and the highest titre was usually obtained within 8 to 14 days after injection; the dilutions used were 1/10, 1/50, 1/100, 1/150, 1/200, 1/250, 1/300, 1/400, 1/500 and 1/600. The sera were left in the incubator at 37°C. for twelve hours, then shaken, left at room temperature for one hour and read; no subdivision (two plus, three plus, etc.) was made, but only complete agglutination considered as positive in a given dilution.

After a high titre had been obtained in any one animal for two titrations two days apart this animal was exposed to the rays of a mercury arc (Hanovia, 110 volt, 5 amp., 25 cm. skin distance) for thirty to ninety minutes daily. The abdomen was shaved two or three days previously with sodium sulphide and the animal, on the day of exposure, strapped on an animal board and placed at a distance of 25 cm. (measured normally

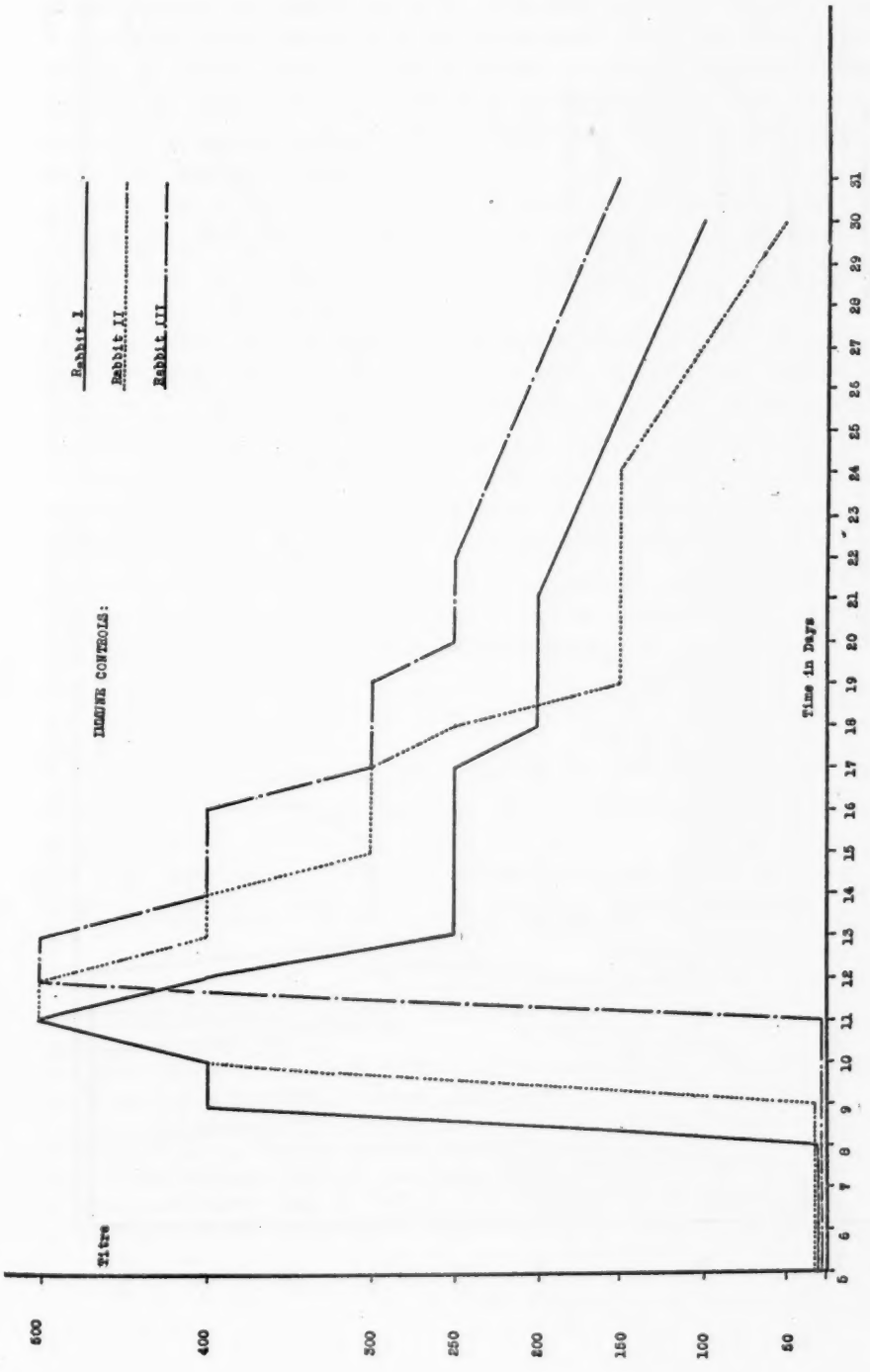

Rabbit I
Rabbit II
Rabbit III
IMMUNE CONTROLS:
Titre
Time in Days
500
400
300
250
200
150
100
50
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

CHART 1

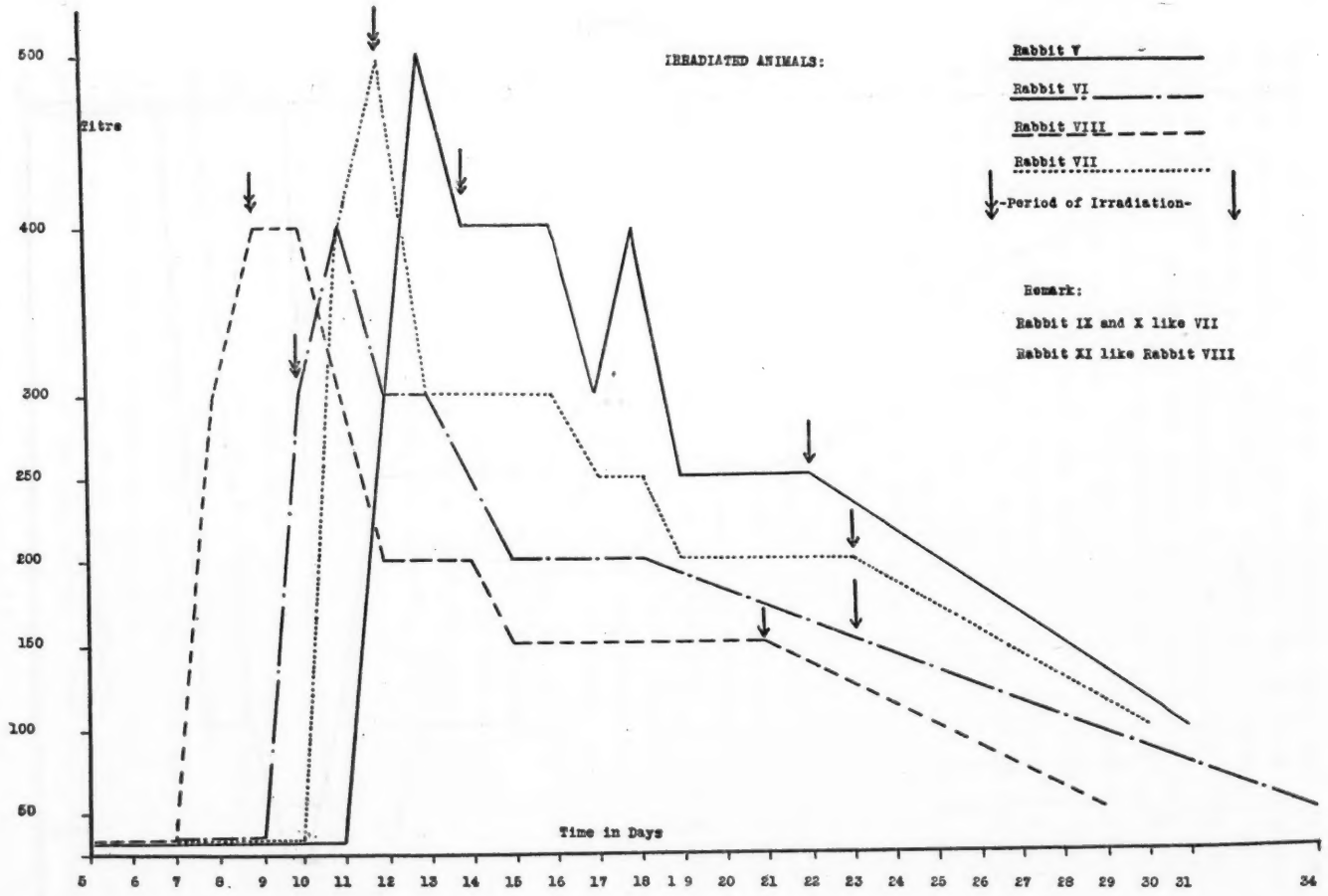

IRRADIATED ANIMALS:
Rabbit V
Rabbit VI
Rabbit VIII
Rabbit VII
-Period of Irradiation-
Remark:
Rabbit IX and X like VII
Rabbit XI like Rabbit VIII
Litre
500
400
300
250
200
150
100
50
Time in Days
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 34

CHART 2

to the mercury arc) under the lamp. The blood samples, not exceeding 2 cc., were taken immediately after exposure; the same animal was always exposed at the same hour of the day so that all titrations during the period of daily irradiation were made 24 hours apart. Three animals were left as immune controls; that is, they lived under the same conditions but were not exposed to light.

The results of this work are given in chart I (controls) and chart II (irradiated rabbits); the time in days is plotted against the highest positive titre. The beginning and end of daily irradiation are indicated by the arrows on chart II.

Chart I shows the irregularity of the agglutinin titre in the untreated rabbit; living conditions of the animals were uniform and rabbits II and III were from the same litter; autospy showed slight induration and irritation of the serosa at the site of injection in rabbits I and III.

The titre curve in chart II remains unchanged in the irradiated animals with the exception of rabbit V; the animal was normal at autopsy on the 31st day after injection. Rabbit IV showed slight ulceration at the site of injection. Rabbit X died (acute pneumonia) on the 27th day. Rabbits VIII and XI showed slight induration at the site of injection. Rabbits VI, VII and IX were normal at autopsy.

CHART 2

CONCLUSIONS

1. Daily irradiations with the mercury arc does not influence the formation of specific agglutinins in rabbits immunized with defatted tubercle bacilli.

2. The titre curves, though showing individual variation, do not differ in duration or height from those of the untreated animal.

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STUDIES WITH ULTRAVIOLET LIGHT[1]

I. THE EFFECT OF QUARTZ-MERCURY-VAPOR IRRADIATIONS (ALPINE QUARTZ-LIGHT) ON EXPERIMENTAL TUBERCULOSIS OF THE CORNEA IN RABBITS

EDGAR MAYER AND MORRIS DWORSKI

Corneal tuberculosis, experimentally produced in rabbits' eyes, is a favorable superficial form of the disease on which to study the local action of ultraviolet radiation. Lupus in patients has been shown to heal under radiations from the carbon-arc lights, after contact pressure-exposures and over prolonged periods; the effective rays were the ultraviolets and violets, inasmuch as most of the others were filtered out. The exact mechanism of the healing process is unknown, but it is probably the result of a combination of successive changes, namely, hyperemia, chemical disturbances, destruction of some bacteria, and local action on the products of the exciting bacteria. Focal reaction seems the most prominent factor, and in its healing effect we are reminded of similar results produced by tuberculin.

In 1885 Baumgarten (1) described the evolution of the corneal tubercle. This tuberculous lesion can be constantly observed and the changes easily noted under different experimental conditions. Lewis and Montgomery (2) have employed experimental corneal tubercle to determine the value of certain therapeutic agents, such as Lugol's solution, calcium lactate, benzol and tuberculin. Passow (3) claims to have shown that artificial light and sunlight, applied directly, can heal tuberculous conjunctivitis and corneal ulcers in patients. Krusius (4) found that a few exposures of altitude and lowland sunlight did not, to any extent, affect the eye lesions of rabbits. The X-ray and thorium also proved unsatisfactory. However, the absence of changes under a few irradiations carries little weight when we realize that with lupus it requires six months of regularly repeated exposures to stimulate healing. Solar radiation does produce increased albumin in the aqueous humor, indicating some organic effect upon the deeper vessels. By

[1] Conducted under fellowships of the Trudeau Foundation, Saranac Laboratory, Saranac Lake, New York.

raying with sunlight immediately after inoculation, Krusius was able to hinder the development of the lesion; but further exposure of the eye did not affect the progress of the disease. The preliminary delay in the disease might have been due to the action of the longer and more deeply penetrating solar rays on the inoculated bacilli.

TECHNIQUE OF INTRACORNEAL INOCULATION

In the authors' experiments a bovine strain of tubercle bacilli of moderate virulence (B1 of the Saranac Laboratory) was the infecting agent. The culture was grown on 5 per cent glycerine broth. The bacilli were emulsified, and the suspension was centrifugalized at high speed to remove clumps. A loopful of the cloudy supernatant fluid contained between 40 and 50 bacilli to the field, singly and in small clumps. The rabbits' eyes before inoculation were thoroughly anesthetized with cocaine. Then, with a sharply pointed eye-scalpel, the corneal margin was split parallel to its surface by lateral incision, producing an opening 2 to 3 mm. long, and care was observed not to puncture the anterior chamber. Into this pocket two loopfuls of the culture were inserted. (The loop was about 2 mm. in diameter.) With this method it was possible to produce a satisfactory corneal lesion.

A mercury-quartz alpine lamp with a burner, 300 hours old, 110 volts, A. C., was the source of the radiation. The spectrum of this radiation shows mostly actinic rays; namely, violet, blue, and ultraviolet. The ultraviolets are of much shorter wave-length than those of the solar spectrum and are the most easily absorbed and very irritating; therefore, pronounced focal reactions were quickly produced. The lamp was run on an alternating current, 110 volts; it was burned to its high point of luminosity (about 10 minutes) before the animals were exposed. Irradiations were first given beginning with 2 to 5-minute exposures at a distance of 10 inches from the burner. The subsequent dosage was determined by the reaction of the eye. The intervals between exposures depended, in most cases, on the subsidence of the eye reaction. The treated eye was held open by the operator and the uninfected eye covered during the irradiation.

PLAN OF EXPERIMENTS

Thirty-two rabbits were used and divided into groups as follows:

Group A: 7 controls, not irradiated.

Group B: 6 irradiated, beginning 24 hours after infection.

Group C: 9 irradiated, beginning 10 days after infection.
Group D: 6 irradiated, beginning 10 days after infection and, in addition, the eye flooded with 1 per cent aqueous solution of eosin during exposure.
Group E: 4 irradiated, beginning 10 days after infection; eye flooded with a saturated aqueous solution of quinine muriate during exposure.

Group A: Development of the corneal lesion in the controls: Observations were made on the eyes without the use of a lens, and under daylight. A somewhat lengthy description will be given of the evolution of the disease in the controls, inasmuch as they will form the basis for describing changes in the treated groups. The period of time quoted for the appearance of the various phases of the disease is an average for the animals observed. The progress of the disease was fairly uniform in the controls. For 24 to 48 hours after inoculation a slight cloudiness persisted in the area of inoculation. The sclera and bulbar conjunctiva appeared normal. The opacity at the point of inoculation in most animals disappeared at the end of 24 hours, and only on careful examination could the incision in the cornea be discerned. There was no change until the eighth day, when the opacity at the point of inoculation reappeared with a beginning area of vascular injection of the conjunctiva adjacent to the portion of the infected cornea. On the 13th day marked opacity, about 2 to 4 mm., indicated the formation of tubercle. The lids and the portion of the conjunctiva adjacent to the area of inoculation were then markedly congested and there was a slight swelling of the cornea. On the 15th day several small whitish points appeared around the larger area of opacity, indicative of metastasis. On the 21st day corneal and circumcorneal vascularization or pannus first appeared, with several small capillaries located at the outermost edge of the cornea. On the 23rd day the centre of the tubercle became caseous and the cloudy area now extended to the pupil. The pannus was enlarged and there was a marked distortion of the cornea. On the 27th day the corneal epithelium over the caseous area broke through, and formed an ulcer with a purulent discharge, as a staphyloma appeared. The progress of the disease continued, so that on the 49th day the entire area of the cornea and pupil was involved. The discharging ulcer was surrounded by a vascular band. There was no tendency to heal spontaneously. On the 126th day the eye presented a mass of ulcerated tissue. This

description was rather typical of the progression of disease in all the control animals.

Group B: Irradiation 24 hours after infection: Irradiation was begun 24 hours after infection in an endeavor to abort the development of the tubercle. This group included two series, group B1 consisting of four rabbits, and group B2 consisting of only two rabbits. Two others died on the eighth day of experiment. The periods and time of exposures are shown in table 1.

TABLE 1

GROUP B1			GROUP B2		
Day of radiation after infection	Time	Distance	Day of radiation after infection	Time	Distance
	minutes	*inches*		*minutes*	*inches*
1	5	10	1	2	10
3	5	10	4	2	10
7	8	10	7	4	10
9	10	10	9	6	10
11	10	10	11	6	10
15	15	10	17	6	10
19	15	10	25	7	10
23	15	10	29	7	10
25	15	10	39	8	10
29	20	10	46	9	10
34	20	10	53	10	10
43	20	10	60	11	10
49	20	10	67	12	10
56	20	10	76	13	10
60	20	10	88	15	10
76	20	10			
Total 213 minutes			Total 118 minutes		

In group B1 the first exposure was five minutes at a distance of 10 inches from the lamp. On the following day the conjunctivae were congested and swollen. When this began to subside (3rd day) the eyes were again exposed. The reaction was then very severe, the vessels in the conjunctivae were very prominent, the lids were inflamed, and an exudate partly closed the eyes. On the 7th day this marked reaction began to subside. Tubercles became evident in this group between the 7th and 9th days, the light producing no inhibitory effects. From then on the disease was progressive, despite radiation, and in two of the ani-

mals it was even more marked than in the controls. Although the irradiations were continued, the eyes were similar in appearance to that of the controls at the end of 60 days. It was evident that the dosage of light employed produced harmful reactions and, instead of a favorable effect in combating the infection, the opposite occurred.

In group B2 a smaller dosage of radiation was administered, and better results were obtained. Though the tubercle developed, its course was much slower. In the rabbit which died on the 74th day, due to an intercurrent infection, a small area of opacity was the only remaining indication of the disease. In the surviving rabbit caseation appeared on

TABLE 2

GROUP C1			GROUP C2		
Day of radiation after infection	Time	Distance	Day of radiation after infection	Time	Distance
	minutes	*inches*		*minutes*	*inches*
10	3	10	11	2	10
12	6	10	15	4	10
14	10	10	18	4	10
19	15	15	25	5	10
33	20	1	29	5	10
45	20	2	39	6	10
67	10	10	46	7	10
73	15	10	53	8	10
80	15	10	60	9	10
			63	10	10
			76	11	10
			89	12	10
Total 114 minutes			Total 83 minutes		

the 27th day and remained localized until the 67th day. No ulceration occurred and this animal died on the 95th day.

Group C: Irradiation begun 10 days after infection: This group was divided into group C1 of 5 rabbits and group C2 of 4 rabbits. The periods and time of exposures are shown in table 2.

In series C1 the increase of dosage was made rather too rapidly and produced marked eye reactions. The disease during the first exposures seemed to be aggravated but, with the subsidence of the signs of focal reaction, the tuberculous lesion gradually lost its inflammatory appearance. The favorable influence of the light was evident in both of these groups. The pannus appeared in all treated animals from the 21st to

the 30th day, being delayed when compared with the 21st day which was the average period of the controls. The light appeared to localize the disease, and there was a definite retardation of the development of secondary tubercles around the caseating focus. In the controls these small whitish areas of secondary tubercles appeared between the 15th and 21st days, while in the treated eyes there was a marked delay and wide variation; for instance, they first appeared on the 21st, 34th, 37th, 39th, 53rd and 74th days. The first signs of healing in most cases came after the 50th day. At this time all of the controls showed gross disease, but the treated eyes began to develop fibrous tissue over the ulcerated surface. Granulation tissue formed, and the focus of caseation was slowly absorbed. The blood vessels, also pannus which had grown over the cornea from the conjunctiva, gradually disappeared. Observations made on the 110th day disclosed that in all treated animals the pannus was no longer present. In 7 animals the caseation had been absorbed, leaving an opaque area on the cornea. The conjunctiva above the area of the infected cornea was corrugated in appearance, due to fibrous tissue. The other three rabbits still showed caseation.

Group D: Irradiation started 10 days after infection: Eye instilled with a 1 per cent aqueous solution of eosin: This group first consisted of 6 rabbits, in which the treated eye was kept flooded with 1 per cent eosin (Gruebler's aqueous solution), during irradiation. Unfortunately 4 animals died of intercurrent diseases early in the course of the tuberculous infection, so that we had only two rabbits for observation. The rationale for the use of eosin in this group and the quinine in *group E* was to sensitize the tissue to light irradiation by a fluorescent substance. Eosin and quinine possess this property. (For tissue sensitization to light, see E. Mayer, AMERICAN REVIEW OF TUBERCULOSIS, 1921, v, 2.) The dose of light was the same as in *group C2*. The disease in the two rabbits was slow in evolution, and healing took place. The lesions did not ulcerate. In the 4 rabbits that died from intercurrent diseases the eye results appeared promising.

Group E: Irradiation started 10 days after infection: Eye instilled with saturated aqueous solution of quinine: Four rabbits were used. The dose of light was the same as for *group C2*. The quinine was applied like the eosin. In two rabbits we had to conclude that the quinine had no effect on the progress of the disease as the course was similar to that in *group C*. However, in the other two rabbits quinine seemed to have a harmful effect, and the disease progressed with no sign of healing, so

TABLE 3

Average time of the appearance of various stages in the evolution and healing of corneal tubercle in all groups

GROUPS	FIRST APPEARANCE OF TUBERCLE AS DENSE CLOUDINESS AT POINT OF INOCULATION	APPEARANCE OF BLOOD VESSELS IN CORNEA (PANNUS)	FIRST APPEARANCE OF CASEATION	APPEARANCE OF SECONDARY OR METASTATIC TUBERCLES	STAPHYLOMA AND ULCERATION	BEGINNING OF ABSORPTION OF CASEATION	HEALING TUBERCLE, GRANULATION AND DISAPPEARANCE OF PANNUS	NONHEALING TUBERCLE
	day	*day*	*day*	*day*	*day*	*day*	*day*	*day*
Irradiation commenced 24 hours after infection	9	23	27	74 (one rabbit)	Absent	60	95	
Irradiation commenced 11 days after infection	9	22	31	43	67	58	110	
Irradiation (plus quinine) commenced 11 days after infection	10	22	21	36	41	In one rabbit no absorption; in the other 82nd day	110 (one rabbit)	110 (one rabbit)
Irradiation (plus eosin) commenced 11 days after infection	10	30	34	49	Absent	58	98	
Controls	9	21	17	18	27	Absent	Absent	110

that on the 110th day the eye was a mass of disease possibly worse than that of the controls.

In a previous experiment, the authors had instilled some tuberculous eyes of rabbits with eosin and quinine almost daily without other treatment, and no effect was produced on the development of the disease. Consequently this control was not repeated in the present series.

EFFECT OF ULTRAVIOLET RADIATION ON THE NORMAL EYES OF RABBITS

It appeared to be important to decide before radiating patient's eyes whether any harm could result to the eye.

Direct ultraviolet radiation from a new quartz-burner to the normal open eyes of rabbits for one hour at a distance of three feet caused no ulceration. Radiation for half an hour at a distance of ten inches caused clouding of the cornea that cleared in three weeks. Three hours after the half-hour exposures, a marked irritation of the conjunctiva and cornea appeared, which gradually increased and after two days the cornea appeared abraded. The inflammation soon receded, but a corneal cloudiness appeared, which persisted until about the 20th day. No further changes were evident after that time.

DISCUSSION AND CONCLUSION

It is evident that in the application of light to a superficial focus of experimental tuberculosis, such as in the cornea, errors may occur which must be avoided to obtain the best results. One factor of importance is the use of the proper number of bacilli for inoculation. Too large an infecting dose sets up a rapidly progressive disease against which radiation is ineffective. If the dose is too small spontaneous healing of the tubercle may follow. Finally, as we have noted, overexposures to untraviolet radiation may irritate instead of heal.

Jansen first mentioned the histological changes in the tubercle of a rabbit's cornea, after exposures to actinic radiation; namely, vascular dilatation, partial thrombosis, destruction of giant and epithelioid cells, followed by a serous and serofibrinous exudate, collections of leucocytes, and, finally, vacuolization and necrosis. In lupus Finsen found, under compression treatment, fewer blood-vessel changes because of less vascularity. Jansen found these effects no deeper than 0.5 mm. The direct destruction of the bacilli themselves in these lesions seems

to play only a minor part, if any, in these exposures. The tissue reaction performs the major rôle in the destruction. Finsen could destroy the bacilli with carbon-arc radiation, through the depth of a rabbit's ear, but only under extreme pressure which caused a dehematization of the tissues. Hemoglobin itself strongly absorbs the actinic rays. Klingmüller and Halberstadt were still able to infect guinea pigs by inoculating them with healing lupus tissue, after it had been treated with carbon-arc radiations. A destruction of some of the bacilli, or an attenuation of them, may have occurred however.

Conjunctival tubercle or phlyctenule possibly responds to radiation much more rapidly, because of the ease of producing focal reaction in that tissue. The cornea itself is avascular, so that the hyperemia induced in it during a focal reaction with light radiation is from the proliferating conjunctival vessels.

It is evident that the question of dosage of light is one that must be worked out experimentally for each tissue. There are too many varying factors to allow us to formulate rules for treatment of an eye tuberculosis with ultraviolet radiation.

In human corneal tuberculosis, Passow reported healing by direct exposures of the open eye. We have had experience with two such cases and the results were favorable. We included partial exposure of the conjunctiva in order to induce a more marked focal reaction. These reactions were very painful, and had to be relieved by cocaine. Similar focal reactions, followed by healing, have of course been induced by tuberculin.

Quinine as a sensitizing substance has strong absorptive power for ultraviolet radiations, and it fluoresces easily. However, it seemed to irritate too much in our few experiments. Macht recently found that exposures of white rats to ultraviolet radiations, following injections of quinine, caused a slightly greater activation of the drug than without such exposures. Eosin seemed to definitely help in our experiments. Gassul and Levy have shown how eosin can sensitize the organs of white mice to ultraviolet radiation. Gyorgy and Gottlieb have also shown it to sensitize the tissues in rickets of children so that it shortened the period of treatment with ultraviolet radiation markedly. We feel, however, that with any local tuberculosis, treated with radiation, the need of always combining local with general body exposures should be emphasized.

CONCLUSIONS

We believe that our experiments show that the ultraviolet light has definitely influenced the healing of the corneal tubercle of rabbits' eyes.

Figures 1 to 4 will show the difference between the controls and the radiated animals.

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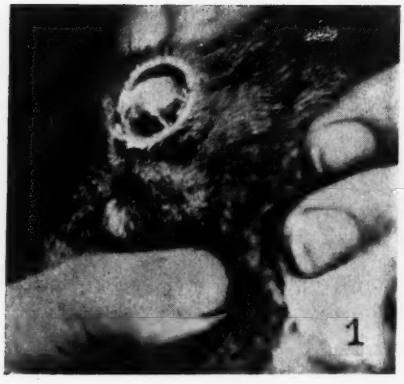

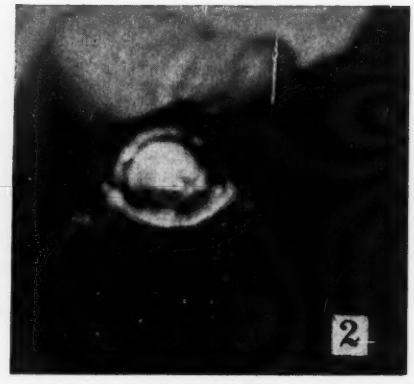

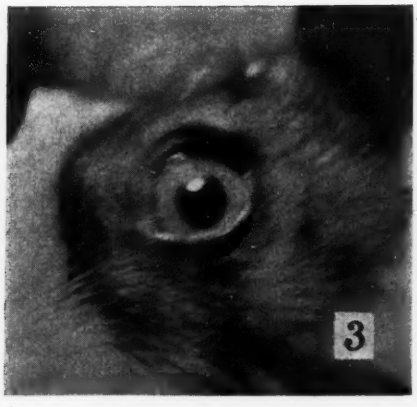

FIGS. 1 AND 2. CASEOUS BOVINE TUBERCULOSIS OF RABBITS' EYES; PROGRESSIVE LESIONS IN UNTREATED TUBERCULOSIS

FIG. 3. BOVINE TUBERCULOSIS OF RABBIT'S CORNEA HEALED BY ULTRAVIOLET IRRADIATIONS COMBINED WITH EOSIN INSTILLATIONS

FIG. 4. BOVINE TUBERCULOSIS OF RABBIT'S CORNEA HEALED, WITH OPACITY, BY ULTRAVIOLET IRRADIATIONS ALONE

STUDIES WITH ULTRAVIOLET LIGHT[1]

II. THE ACTION OF QUARTZ-MERCURY-VAPOR IRRADIATION ON INHALATION TUBERCULOSIS IN PRIMARILY INFECTED AND SENSITIZED GUINEA PIGS

EDGAR MAYER AND MORRIS DWORSKI

Ultraviolet irradiation has been variously viewed by clinicians in its effect on pulmonary tuberculosis. Some enthusiasts, such as Augsten, König, Aschenheim and Weill, have strongly advocated it. For the most part, however, it has been considered only as an adjuvant, of little value except for nonpulmonary tuberculosis, in which it has proved its greatest usefulness. Efforts to investigate the problem have thus far been disappointing in results.

Only a few experiments have been carried out with animals. Rohde reported a series that had most unconvincing results. He inoculated twelve 300 gm. guinea pigs with 1 cc. of a saline emulsion of tuberculous sputum and then radiated the shaved animals with the Alpine lamp. The radiated guinea pigs showed no gross tuberculosis, and microscopically only an occasional tubercle one month after infection, whereas the controls had marked cachexia and widespread tuberculosis of the liver and spleen with caseation of the lungs, peritoneum, inguinal lymph nodes and pelvis. Rohde concluded that the radiation had a very marked influence in hindering the development of the infection. On the other hand, Hase conducted similar experiments, with negative results. Recently, Gassul, in presenting this work, tries to explain the contradiction in results by claiming that Hase employed too large a dose of highly virulent tubercle bacilli for his animals and therefore could not expect favorable results.

In view of the conflicting statements our experiments were planned with the hope of something more definite being determined. It was planned to radiate shaved and unshaved animals. With rickets in rats it has been found unnecessary to shave animals when treating them with ultraviolet radiation, in order to bring about clinical healing and

[1] From the Saranac Laboratory, Saranac Lake, New York.

an increase in inorganic phosphorus. However, in malaria of birds, Whitmore induced relapses by light exposure much more easily when only a small area of skin was shaved than when all feathers were intact. Lutz showed that, histologically, the same changes occurred under ultraviolet radiation in the skin of guinea pigs as in human skin. Kestner, however, with dogs, was unable to produce an erythema with one-hour exposures at twenty inches. With our guinea pigs and rabbits we were well able to obtain both erythema and desquamation on shaved areas. The darker skin of rabbits eventually formed good pigmentation. It was decided with our guinea pigs to employ intracutaneous tuberculin injections as guides to allergy tests, which are considered as closely correlated with the extent of disease in guinea pigs. The dosage of radiation had to be given empirically, there being no particular guide, but it was aimed to maintain a mild erythema. During exposures the eyelids protected the conjunctiva satisfactorily. Other experiments, now being carried out, will aim to solve the question of production of focal reactions in pulmonary tuberculosis when an overdose of radiation is given.

PRIMARY GROUP I

Eighteen guinea pigs were first used. An inhalation infection was made as described by Baldwin and Gardner in the AMERICAN REVIEW OF TUBERCULOSIS, August, 1921, p. 446. A strain of moderate virulence (H37 of Saranac Laboratory) was the infecting microörganism, and the suspension contained 6 to 10 bacilli to a field when a loopful was spread over an area 20 mm. in diameter. The animals were divided into three subgroups of 6 each: *I-1*, to be irradiated daily, immediately after infection; *I-2*, seventeen days after infection; and *I-3*, the controls. Nine were shaved every few days over the greater part of the back; nine others were unshaved. The first exposure was for 10 minutes at a distance of $1\frac{1}{2}$ feet from the lamp. It was repeated daily but increased five minutes until two hours' radiation, the maximum exposure, was given. Each subgroup received 31 consecutive daily exposures. Intracutaneous skin tests were made at intervals, 17 days after infection, and later, using 0.1 cc. of 5 per cent O. T. The animals were killed and autopsied 58 days after infection. The source of radiation was an Alpine Lamp, 110 volts, A.C., with a burner of 400 hours usage.

TABLE 1

Skin reactions of subgroup I-1 (single infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	−	+	+	+++	++	++
2	+	−+	+++	++++	+++	+++
3	+	+	++	+++	++	+++
4	−	−+	+	+++	++	++
5	+	+	++	++++	++	+++
6	+	+	++	+++	+++	+++

TABLE 2

Skin reactions of subgroup I-2 (single infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	+	+	+++	+++	+++	++++
2	−	−	−	++	++	+++
3	+	+	+	+++	+	++
4	−	−	+	++	++	+++−
5	+	+	+	++	++	+++
6	+	−	+	+++	+++	+++

TABLE 3

Skin reactions of subgroup I-3 (controls—single infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	−	−	+	++	++	++
2	−	−	Died			
3	+	+	++	+++	++	+++
4	+	+	+	+++	+	+++
5	+	+	++	++	++	++
6	−	−	+	+++	+++	+++

Classification of Intracutaneous Tests

∓: Doubtful

+: Erythema or induration, 10 mm. × 10 mm., occurring 24 to 48 hrs. after injection, persisting and gradually fading

++: Erythema and induration

+++: Erythema or induration with central ulceration

++++: Erythema or induration with marked ulceration

TABLE 4

Autopsies of animals infected once by inhalation

GROUP	GUINEA PIG NUMBER	LYMPH NODES							SPLEEN	LIVER	LUNGS	DAYS AETER INFECTION
		Superficial inguinal	Deep inguinal	Retro-peritoneal	Tracheo-bronchial	Bronchial	Cervical	Iliacs				
I-1	1	0	0	+	+	0	0	0	++	0	++	59
	2	+	+	+	+	+	+	+	+++	++	++	59
	3	++++	++++	+++	++++	+++	+++	++++	++++	++++	++++	59
	4	+++	+++	++	++++	++	++	+++	++++	+++	++++	59
	5	++	+++	+++	+++	++	+++	+++	++++	++++	++++	59
	6	+++	+++	+++	+++	++	++	+++	++++	++++	++++	59
I-2	1	++	+	+	++	+	0	+	+	+	++	59
	2	++	+	+	++	0	−	+	++	0?	+++	59
	3	+++	+++	++	++	+	+	++	++	+	+++	59
	4	++	++	+	+++	+	+	++	+++	+++	++++	59
	7	++	++	++	++	+	+	+++	+++	+++	++++	59
	6	+++	++	++	++	+	+	++	++	++	+++	59
I-3	1	+	+	+	++	0	0	+	++	+	+++	59
	2	+	+	+	++	0	0	+	++	+	++	59
	3	++	++	+	++	+	0	++	+++	++	++++	59
	4	++	++	+	++	0	0	+	++	+	+++	28
	5	++	++	+	++	+	+	+	++	++	+++	59
	6	++	++	+	++	0	+	+	+++	++	+++	59

Classification

Lymph Nodes:

\+ = sl. enlarged and hard
++ = enlarged and caseous
+++ = enlarged; firmer and fibrocaseous
++++ = enlarged and caseous almost throughout

Organs (lungs, liver and spleen):

\+ = isolated tubercle
++ = enlarged organ with scattered tubercles
+++ = enlarged with conglomerate tubercles
++++ = enlarged and studded with tubercles in stage of caseation.

RESULTS

The findings from the intracutaneous reactions are given in tables 1, 2 and 3, and the autopsy changes in table 4. The course of the disease was apparently not modified by the radiation and the skin tests were uniformly positive in both control and treated animals.

SENSITIZED GROUP II

Eighteen guinea pigs were used and divided into three subgroups similar to those of the foregoing experiment. All were sensitized by receiving 0.5 cc. of a suspension of R1 culture (2 to 6 bacilli to the field). R1 is a human tubercle bacillus of very low virulence for guinea pigs when inoculated subcutaneously. In subgroup II-1 irradiation was begun immediately after infection. Exposures were made first for 10 minutes at 1½ ft. from the lamp and were increased 5 minutes daily until an exposure of one hour was reached, and thereafter irradiations were given daily for an hour for 32 days. In subgroup II-2 irradiation was begun 17 days after infection, and then succeeding exposures were made similar to those of subgroup II-1. Subgroup II-3 made up the controls. Thirty-two days after primary infection, all animals were reinfected by inhalation, with H37 according to our procedure with the primary-infection group. Irradiation was then increased daily 5 minutes in subgroups II-1 and II-2 until two hours' exposure was reached, and so continued until 31 days after the inhalation infection.

Intracutaneous tests were made, at intervals, 17 days after infection and later. The animals were killed and autopsied 72 days after the primary infection. The records of the intracutaneous tests are given in tables 5, 6 and 7 and the autopsy findings in table 8.

RESULTS

The intracutaneous reactions at 52 and 58 days were less marked in all treated animals but one, and the extent of tuberculous involvement as shown in table 8 was similarly less than in the primary-infection group.

From this series of experiments it is inferred that ultraviolet irradiation did modify the course of tuberculous infection in guinea pigs, and perceptibly the allergic reaction, as manifested by the intracutaneous tests.

TABLE 5

Intracutaneous reactions of subgroup II-1 (double infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	−	+	++	++	+	+
2	−	++	++	++	+	+
3	−	++	++	++	+	+
4	+	++	++	++	+	+
5	−	+	+	++	+	+
6	+	+	++	++	+	+

Reaction positive at 24 days.
Reaction at 52 and 58 days lessened.

TABLE 6

Intracutaneous reactions of subgroup II-2 (double infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	+	+	++	++	+	+
2	−	++	+	++	+	+
3	−	++	++	++	++	+
4	+	++	++	+++	+++	+++
5	−	+	++	++	+	+
6	−	+	++	++	+	+

Cutaneous reaction lessened at 52 and 58 days except in guinea pig 4.

TABLE 7

Intracutaneous reactions of subgroup II-3 (controls—double infection, inhaled)

GUINEA PIG	17 DAYS AFTER INFECTION	24 DAYS AFTER INFECTION	29 DAYS AFTER INFECTION	34 DAYS AFTER INFECTION	52 DAYS AFTER INFECTION	58 DAYS AFTER INFECTION
1	−	−	+++	+++	+++	+++
2	+	++	++	++++	+++	+++
3	−	++	++	++	+	+
4	−	++	++	++	+++	+++
5	−	+	++	+++	+++	+++
6	+	+	++	++	+++	++

Controls show no diminished reaction except in guinea pig 3.

ACTION OF ULTRAVIOLET IRRADIATION ON TUBERCULOUS GUINEA PIGS INFECTED SUBCUTANEOUSLY

Sixteen guinea pigs were infected subcutaneously in the right groin with 1 cc. of an emulsion containing 2 to 6 bacilli to the field (H37). The animals were divided into three subgroups, two to be irradiated and one control group. Group 1 was irradiated immediately after infection, beginning with five-minute exposures, 1½ ft. from the lamp,

TABLE 8

Autopsies of sensitized animals (double infection—inhaled)

GROUP	GUINEA PIG NUMBER	LYMPH NODES							SPLEEN	LIVER	LUNGS	DAYS AFTER INFECTION
		Superficial inguinal	Deep inguinal	Retro-peritoneal	Tracheo-bronchial	Bronchial	Cervical	Iliacs				
II-1	1	++	++	0	++	0	0	0	0	0	0	72
	2	++	++	+	++	0	0	+	0	0	+	72
	3	0	0	+	+	0	0	0	0	0	0	72
	4	0	0	+	+	0	0	0	0	0	0	72
	5	+	0	0	++	0	0	0	+−	0	0	72
	6	+	0	0	+	0	0	0	+	0	0	72
II-2	1	+++	+++	++	+	0	0	++	0	0	0	72*
	2	++	++	+	+	0	0	+	0	0	0	72
	3	++	++	+	+	0	0	+	0	0	+	72
	4	+++	+++	+++	+++	+	+	+++	++	+	++	72
	5	+	0	0	+	0	0	+	0	0	0	72
	6	+	0	0	+	0	0	0	+	0	0	72
II-3	1	++	++	++	++	+	+	++	++	++	+	72
	2	+	+	+	+	++	+	++	+	+	+	72
	3	+	+	0	+	0	0	+	0	0	0	72
	4	+	+	+	+++	++	+	+	+	0	+	72
	5	+	++	+	++	+	+	++	+	++	+	72
	6	+	+	+	+	+	0	++	+	++	+	72

*Chronic pneumonia.

and increasing daily for 5 minutes until 2 hours' irradiation was reached. This maximum exposure was continued until 54 days after infection. Irradiation was begun in group 2, 17 days after infection and was given in the same manner as in group 1, two hours being the maximum dose. Group 3 was the control. Intracutaneous tests were made at intervals from 22 days after infection onward, using 0.1 cc. of a 5 per cent solution of O. T. The animals were killed and autopsied 54 days after infection. (Tables 9 to 12.)

RESULTS

The autopsy findings showed no material difference between the exposed animals of group 1 and the controls of group 3. However, guinea pigs 1 and 2 of group 2, which received treatment 17 days after infection, had a very small amount of disease, and in guinea pig 3 of

TABLE 9

Skin reactions of group 1 (single infection, subcutaneous)

GUINEA PIG	22 DAYS AFTER INFECTION	28 DAYS AFTER INFECTION	32 DAYS AFTER INFECTION	38 DAYS AFTER INFECTION
1	+	++	+++−	+++
2	++	++	+++−	+++
3	++	++	+++−	+++
4	+	+	+++−	+++
5	+	++	+++	++
6	+	++	++	+++

TABLE 10

Skin reactions of group 2 (single infection, subcutaneous)

GUINEA PIG	22 DAYS AFTER INFECTION	28 DAYS AFTER INFECTION	32 DAYS AFTER INFECTION	38 DAYS AFTER INFECTION
1	+	+	+	+
2	+	+	+	+
3	+−	0	0	+−
4	+	+	++	++
5	+	++	++	++

TABLE 11

Skin reactions of group 3 (controls—single infection, subcutaneous)

GUINEA PIG	22 DAYS AFTER INFECTION	28 DAYS AFTER INFECTION	32 DAYS AFTER INFECTION	38 DAYS AFTER INFECTION
1	+	+−	++	++
2	+−	+	++	+++
3	0			
4	+	+	+	+++
5	+	+	+	+++

group 2 no macroscopic tuberculosis was evident. To attribute this suppression of infection to ultraviolet irradiation, and yet to find the extensive disease in group 1 and in guinea pigs 4 and 5 of group 2, is hardly a permissible explanation. Lack of infection was probably due to some error in technique.

TABLE 12

Autopsies of guinea pigs infected subcutaneously

GROUP	GUINEA PIG NUMBER	LYMPH NODES							SPLEEN	LIVER	LUNGS	DAYS AFTER INFECTION
		Superficial inguinal	Deep inguinal	Retro-peritoneal	Iliacs	Tracheo-bronchial	Bronchial	Cervical				
1	1	+++	+++	++	++	++	+	+	++	+	+	54
	2	++	++	+	+	+	0	0	+	+	+	54
	3	+++	+++	+++	++	++	0	0	++	+	0?	54
	4	+++	+++	++	+	+++	0	0	+	++	+?	54
	5	++	++	++	0	++	+	+	++	+++	+	54
	6	++	++	++	0	++	+	+	++	++	+	54
2	1	+	+	+	+	+	0	0	0	0	+	54
	2	0	0	+	0	0	0	0	+	0	0	54
	3	0	0	0	0	0	0	0	0	0	0	46
	4	++	+++	+	+	+++	+	+	++	+	+	54
	5	++	++	+	+	++	+	+	++	++	++	54
3	1	++++	++++	+++	+++	++	+	+	++	+++	++	54
	2	+++	+++	+++	+++	++	+	−−	+	+++	++	54
	3	Died 11 days after infection										
	4	++	++	++	+	++	+	+	++	++	++	54
	5	++	+++	+	+	+++	+	+	+++	++	+++	54

CONCLUSIONS

Under the conditions of inoculation used in the foregoing animals, it cannot be concluded that the experimental tuberculosis of guinea pigs was materially influenced by the irradiations. The intracutaneous reactions correlated rather closely with the autopsies, and both indicated, with few exceptions, steady progression of the disease.

From the findings no conclusive deductions can be made upon the use of light irradiations in patients. Too many varying factors prevent this.

STUDIES WITH ULTRAVIOLET LIGHT[1]

III. THE BACTERICIDAL ACTION OF MERCURY-QUARTZ-VAPOR LIGHT IRRADIATION

EDGAR MAYER AND MORRIS DWORSKI

All rays of both the visible and invisible spectra possess heat, light and chemical properties, but it is chiefly to the violet and ultraviolet rays that chemical action is attributed. It remained for Downes and Blunt to first demonstrate that these rays were especially bactericidal. Koch and Krattenbacher soon verified this; and since then numerous workers have studied this action upon various microörganisms (Browning, Russ, Jones and VanderLingen). Wiesener alone reported that the infrared wave-lengths were as strongly bactericidal as the ultraviolets, but, on repetition, others could not verify this. It has been shown that with ultraviolet rays the bactericidal effect increases with the diminution of the wave-length and the increased frequency of the vibrations. Changes in the H-ion concentration seem to play no part. Increase in temperature of the surrounding medium of the microörganisms may enhance the bactericidal action. Harris and Hoyt have demonstrated that particularly the amino-acid radicles of the bacteria absorb rays and so cause bacterial death. It is very probable that there is selective action on the part of different wave-lengths for special bacteria. Conflicting reports have been made on the effect of radiation on bacteria, and especially so with the action of sunlight on tubercle bacilli in sputum. The required period of destruction has been reported to vary from a few minutes to 48 hours. The factors that may affect the result are many: altitude, season, humidity and time of day, suspension-state of the bacteria, thickness of the emulsion of sputum, dry or wet state of bacteria, reflecting power of the environment (such as snow or water), temperature, etc. Henri has shown that ultraviolet rays can render tubercle bacilli non-acid-fast.

It has been our aim to study the action of radiation from a quartz-mercury-vapor light upon suspensions of tubercle bacilli and other

[1] From the Saranac Laboratory, Saranac Lake, New York.

microörganisms. It was planned also to learn the effect on bacteria suspended in circulating blood. It is realized that hemoglobin has particular absorptive power for ultraviolet and other wave-lengths from this source of light, but it was held that the chemical changes occurring in this absorption might in themselves induce bacterial destruction in the blood-stream. Various sensitizing substances can be employed in combination with longer wave-lengths applied to the blood and possibly induce unknown chemical changes. It is impossible to isolate the various

TABLE 1

Exposures of tubercle bacilli to quartz-mercury-vapor radiations (intracutaneous tests)

GUINEA PIG	TIME OF EXPOSURE OF BACILLI TO RADIATIONS	SKIN TEST AFTER 8 DAYS INFECTION	SKIN TEST AFTER 12 DAYS INFECTION	SKIN TEST AFTER 17 DAYS INFECTION	SKIN TEST AFTER 31 DAYS INFECTION
1	3 minutes at 5 inches	0	0	0	0
2		0	0	0	0
3	5 minutes at 5 inches	0	0	0	0
4		0	0	0	0
5	10 minutes at 5 inches	0	0	0	0
6		0	0	0	0
7	15 minutes at 5 inches	0	0	0	0
8		0	0	0	0
9	25 minutes at 5 inches	0	0	0	0
10		0	0	0	0
11	Control: No exposure of bacilli	0	0	Positive	Positive
12		0	0	Positive	Positive
13	Control: No exposure	0	0	Positive	Positive
14		0	0	Positive	Positive

wave-lengths of the quartz-mercury-vapor spectrum without diminishing the intensity of the separate divisions so markedly as to lose bactericidal effect.

1: A saline emulsion of tubercle bacilli (H37) was made up as follows: Bacilli were thoroughly titrated and then centrifugated at high speed to remove clumps. A loopful of the resulting mixture contained 2 to 8 bacilli to the field when spread over an area of 20 mm. diameter. One-tenth cc. thoroughly spread out with a platinum loop was placed in a series of watch-glasses suspended in cold water to prevent desiccation

from the heat of the light. Exposures were made for varying periods, at a five-inch distance, to the rays of an Alpine lamp, whose burner was about 300 hours old. Table 1 shows the periods of exposure and the results of guinea-pig inoculations, together with intracutaneous tests. It is seen that the quartz-mercury-vapor irradiations proved bactericidal in this suspension after a three-minute exposure at a distance of five inches from a 300-hour burner. To attain its maximum intensity, the lamp was burned for fifteen minutes before exposures were made.

TABLE 2

Quartz-mercury-vapor irradiations of suspensions of tubercle bacilli and quinine (intracutaneous tests)

GUINEA PIG	TIME OF EXPOSURE OF BACILLI TO ULTRAVIOLET RAYS—ULTRAVIOLET AND QUININE	SKIN TEST 8 DAYS AFTER INFECTION	SKIN TEST 12 DAYS AFTER INFECTION	SKIN TEST 17 DAYS AFTER INFECTION	SKIN TEST 31 DAYS AFTER INFECTION
1	2 minutes at 5 inches	0	0	0	Positive
2		0	0	0	Positive
3	5 minutes at 5 inches	0	0	0	Positive
4		0	0	0	Positive
5	10 minutes at 5 inches	0	0	0	Positive
6		0	0	0	Positive
7	15 minutes at 5 inches	0	0	0	Positive
8		0	0	0	Positive
9	25 minutes at 5 inches	0	0	0	0
10		0	0	0	0
11	No exposure (controls)	0	Positive	Positive	Positive
12		0	Positive	Positive	Positive
13	No exposure (controls)	0	Positive	Positive	Positive
14		0	Positive	Positive	Positive

Draughts were avoided in the room and a temperature of about 70°F. was maintained.

The guinea pigs were killed at the end of 40 days. No tuberculosis was evident on gross examination of the organs of animals 1 to 10. The other four (11 to 14) showed tuberculosis well scattered through the lungs, spleen, liver and lymph nodes.

2: Quinine, a fluorescent substance, shows strong absorption for ultraviolet rays, and emits violet light. Often such fluorescent substances can

sensitize tissues and cause a changed action of light. The following test was therefore carried out to observe any variation in effect upon tubercle bacilli:

A saturated aqueous solution of quinine was prepared, and 1 cc. was mixed thoroughly with 1 cc. of the solution of the tubercle-bacilli suspension. Exposures were made for various periods, and skin tests were made after guinea-pig inoculations (table 2). Autopsies at the end of 40 days showed tuberculosis in all but guinea pigs 9 and 10.

It required a twenty-five-minute exposure to destroy the tubercle bacilli when mixed with quinine. The absorptive power of quinine for ultraviolet rays may possibly account for this. In experiments carried out by the writers, with direct exposures of quartz-mercury-vapor irradiations to corneal tuberculosis in rabbits, quinine interfered with healing also. No exact explanation can be given.

STUDIES WITH ULTRAVIOLET LIGHT

IV. THE BACTERICIDAL EFFECT OF MERCURY-QUARTZ-VAPOR LIGHT IRRADIATION OF BLOOD CIRCULATING IN VITRO

MANFRED GUTTMACHER AND EDGAR MAYER

THE BACTERICIDAL ACTION OF QUARTZ-MERCURY-VAPOR LIGHT RAYS ON BACTERIA CIRCULATING IN BLOOD OUTSIDE THE BODY

These experiments were planned to learn the effect of radiation applied directly to bacterial suspensions flowing through a quartz-chamber. This aimed to imitate the capillary bed of the blood-stream. No preconceived ideas as to the possible action of the various wave-lengths of the light upon bacterial suspensions in blood were held. Only a brief report of some few preliminary steps of the study can now be made.

Blood-serum absorbs most of the actinic wave-lengths of light, due chiefly to its amino-acid content (tyrosin and tryptophane). Hemoglobin will also absorb these and almost all wave-lengths below 450 $\mu\mu$. However, in the process of absorption many chemical changes may occur, the exact nature of which is not clearly understood. If one cannot conceive of any direct action of the rays employed upon the suspended bacteria, yet limitations to the life of the bacteria may be expected from physical or chemical changes that the rays can bring about in the blood and in the tissue resistance of the animal.

Figure 1 represents a sketch of an apparatus arranged for irradiating the flowing blood, as it passes through a quartz-chamber. Quartz has been found to permit the penetration of almost all of the shorter wave-lengths, while glass absorbs them. The source of light was an Alpine light (quartz-mercury-vapor) of 110 volts, A.C., with a burner of about 100 hours' usage.

The quartz chamber employed had five capillary divisions, each less than 1 mm. in diameter. This contained the thinnest layer of blood at any moment, and therefore allowed as complete penetration of such rays through blood as was possible at any time. However, complete absorption of actinic rays by hemoglobin of the blood interferes with

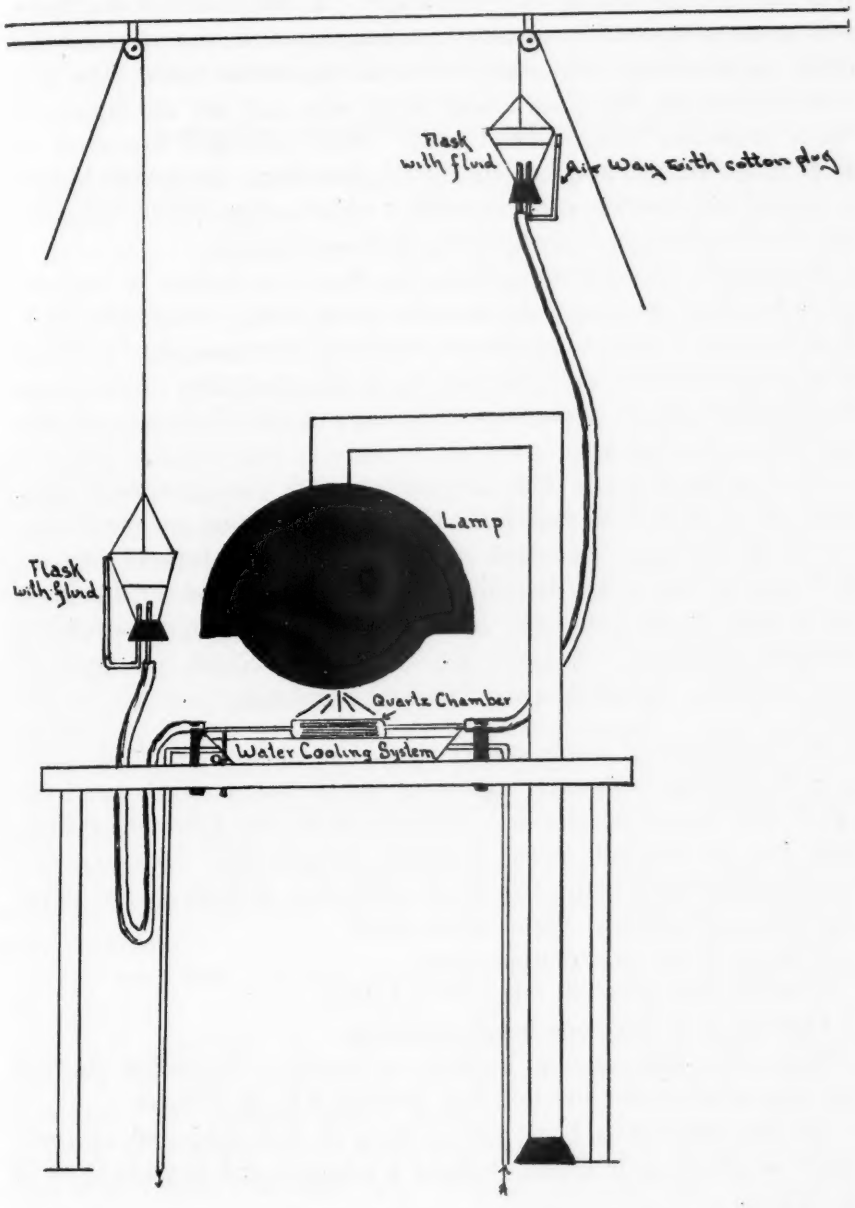

FIG. 1. APPARATUS FOR THE *in vitro* IRRADIATION OF A BACTERIAL SUSPENSION IN BLOOD

penetration even through such thin layers. To obtain a flow, the flasks were reversed in position, so that the circulation of the blood in the body could be simulated. Of course, such an experiment could take into consideration the blood as a body fluid only, and not the factors of tissue resistance of an animal body. With prolonged exposures of mercury-quartz radiation to the blood, heat from the quartz-burner interfered with the flow, and, as a result, a water-cooling system maintaining the chamber near body-heat was used as a support.

The sources of radiation employed in these experiments did not include many of the longer and therefore more deeply penetrating rays. It is planned to use later additional sensitizing substances for the blood, which might provoke chemical changes on the application of the longer wave-lengths and to employ quartz tubing of larger diameter. X-rays are also to be employed.

Some preliminary *in vivo* experiments with the quartz-chamber, inserted as a functional unit of the blood-stream of dogs and sheep were attempted, using anti-coagulants such as sodium citrate, heparin, peptone, and hirudin. However, these were unsuccessful, because clotting interfered, due to the extremely small diameter of the quartz-capillary network.

RADIATION OF A SALINE SUSPENSION

Stock cultures of staphylococci planted in about 150 cc. of sterile meat-broth were constantly incubated for 27 hours. Five cc. of the broth after thorough agitation, were introduced into Erlenmeyer flasks with 525 cc. of sterile saline solution. Immediately thereafter, preradiation agar-petri plates were made, with 2 cc. of fluid, and at stated intervals postradiation plates were made.

Plate A: 2 cc. preradiation plate.

Plate B: 2 cc. after 20 minutes' radiation.

Plate C: 2 cc. after one hour's radiation.

With this suspension of bacteria, a complete circulation through the apparatus in one direction was completed in 2½ minutes.

The bacteria before being put in plate B were subjected to about eight radiations at intervals of about 3 minutes, and in plate C to 24 radiations.

Result: Radiation of the saline solution containing staphylococcus aureus was considerably bactericidal. In the preradiation plate, the colonies were so close that no square millimetre could be found without

colony formation; after twenty minutes' radiation the colonies were still numerous, but perhaps half as frequent as above; after one hour few large colonies and less than one dozen small ones were seen.

RADIATION OF BACTERIA SUSPENDED IN BLOOD

Several of these experiments were carried out but the following mentioned is a typical protocol:

Blood from a dog killed by CO was run into an aseptic 250 cc. Erlenmeyer flask with 25 cc. of 2.5 sodium oxalate. The oxalate was needed because it had been observed in collecting livers for making heparin that the carbon-monoxide blood in the liver had definitely clotted in the vessels. The blood was brought to the laboratory at 11 A. M., and was incubated after the first blood-plate was made with 4 cc. of blood.

At 9 P.M. (ten hours later) the blood, after being strained, was introduced into the quartz-glass chamber. A plate was then made to determine, by comparison with the first, the readiness with which the bacteria grew in blood with carbon monoxide and with sodium oxalate. In a half-hour a second plate was made, and 1 hour and 10 minutes later a final plate.

Results: (1) Blood obtained at the dog-pound under poor asepsis and immediately plated at 11 A.M. showed 30 surface colonies, 15 of which were very large, 3 medium and 12 very small.

(2) The preradiation plate, after 10 hours (1 cc.), showed similarly large surface colonies, the number not diminishing with carbon monoxide and sodium oxalate.

(3) After 30 minutes' radiation, the average for one-way flow through the quartz-chamber being 7 minutes, there were in 1 cc. about 100 colonies (an increase).

(4) After 1 hour and 10 minutes' radiation of 1 cc. there were about 20 colonies.

It was concluded that the contaminating microörganisms found, such as the flora of dog's hair, dirt, etc., did not multiply in carbon-monoxide and sodium-oxalate blood.

After 30 minutes' radiation, however, colonies were more numerous, but after 1 hour less numerous. These results were not satisfactory because the Proteus microörganisms grew all over some plates, dragging colonies along, or inhibiting them greatly and giving discordant results. Therefore, other experiments, a typical protocol of which follows, were carried out:

About 350 cc. of blood withdrawn from a dog was incubated with 5 cc. of a 7-hour broth transfer of staphylococcus aureus. Twenty-four hours later it was rayed as close to the chamber as possible. Charring of blood was prevented by the water-cooling circulation below. The temperature was maintained at 30° to 40°C. The largest diaphragm of the metal globe around the quartz-burner was used. Two hours and 40 minutes of radiation were used.

Result: In none of the plates was any progressive bactericidal action seen. The same blood that was used in this experiment was used in the next, but the lamp that was used was opened completely and exposed at 3 cm. from the quartz-chamber. The average circuit flow in these experiments was 5 minutes. The cultures before radiation could not be distinguished from those radiated for 1 hour and 20 minutes and 2 hours and 40 minutes; they showed mixed growth, chiefly of staphylococcus.

CONCLUSIONS

These experiments are offered only as introductory work to determine what physical, chemical, or physicochemical changes may take place in radiated circulating blood. So far, whatever such changes are that can be produced by the radiation, they cannot destroy staphylococcus aureus microörganisms, when these are mixed with blood flowing *in vitro* and directly exposed to the wave-lengths present in quartz-mercury-vapor light radiations in the procedure outlined. However, when the same microörganism is suspended in flowing saline solution and radiated, these wave-lengths are definitely bactericidal.

Thanks are expressed to Mr. Robert Salinger for his help in this work.

A GRAPHIC METHOD OF REPORTING CHEST ROENTGENOGRAMS[1]

JOHN W. WEBER

An excellent detailed description of the chest roentgenogram often fails to visualize satisfactorily the pulmonary shadows, while one's mental image of them, from the ordinary routine description, is likely to be decidedly hazy. This is particularly true when the shadows show considerable variation in appearance and distribution.

The advantages of the graphic method for recording physical findings in the chest suggested that this procedure might also be advantageously employed in reporting chest roentgenograms. The method evolved has been used by us for the past three years and apparently is preferable to the customary written interpretation.

The familiar symbols for recording the physical examination have been retained in so far as this was feasible, while rough sketches have been utilized to depict the roentgenographic shadows where this seemed desirable. Marginal notations are also occasionally employed. The graphic chart may be supplemented by a brief, summarized written description, although this is not essential for ordinary routine interpretation.

The graphic method is especially advantageous when terms, descriptive of the shadows rather than of pathological changes, are employed in interpretation. It may be used for portraying nontuberculous as well as tuberculous conditions, and conveys, almost at a glance, a fairly precise idea of the character and distribution of the radiographic shadows.

For the sake of brevity, numerous symbols and sketches have been incorporated in each of the appended graphic charts.

[1] From the New York State Hospital for the Treatment of Incipient Pulmonary Tuberculosis, Ray Brook, New York.

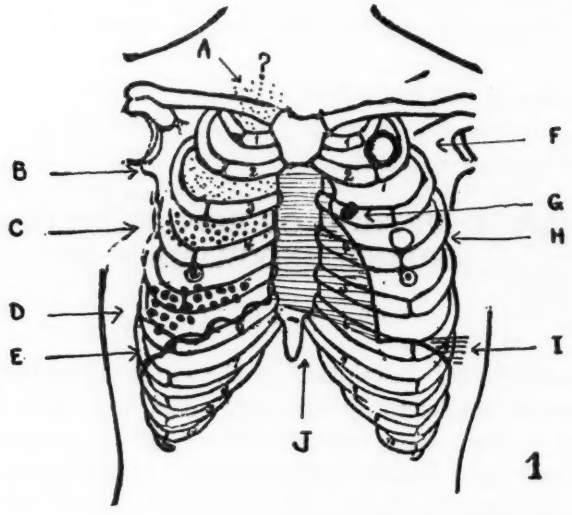

CHART 1

A: Questionable fine mottling: fine dots and question mark (?). *B:* Definite fine mottling: fine dots. *C:* Moderately dense mottling: moderately heavy dots. *D:* Very dense mottling: very heavy dots: the amount of mottling may be indicated roughly by the number of dots used. *E:* Sketch of irregular diaphragm. *F:* Sketch of cavity. *G:* Sketch of dense nodular root shadow. *H:* Sketch of annular shadow. *I:* Haziness of costophrenic sinus: light parallel lines: similar lines of varying thickness may be used to indicate haziness in any portion of the picture. *J:* Sketch of heart.

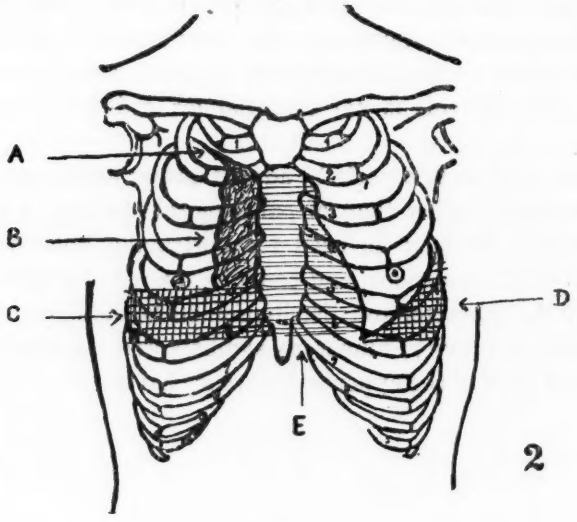

CHART 2

A: Sketch of adhesion. *B:* Sketch of partially collapsed lung. *C:* Fluid: cross-hatching with horizontal upper border. *D:* Simple effusion; cross-hatching with concave upper border. *E:* Heart.

REASONS FOR THE FREQUENT OCCURRENCE OF TUBERCULOSIS AT THE APICES OF THE LUNGS[1]

JOSEPH WALSH

There are two main reasons for the occurrence of tuberculosis at the apices much more frequently than elsewhere in the lungs: (1) the mechanical activity of the apices, and (2) the physical conformation of the bronchial tubes allowing tubercle bacilli to reach the apices, especially the right apex, more readily than other parts of the lungs.

1. THE MECHANICAL ACTIVITY OF THE APICES

So universal are the writings on the inactivity of the apices compared with other parts of the lungs that it is unnecessary to quote the authors by name, yet the arguments proving the opposite appear to me still the stronger. These arguments for the greater activity of the apices are based on (1) therapeutics, (2) bacteriology, (3) physical signs, (4) macroscopic anatomy, (5) microscopic study of the alveoli in different parts, and (6) physics.

1: Therapeutics: All our experience with tuberculosis goes to show that rest of a part affected is a definite aid toward cure and the modern treatment is based more on this than any other single factor. The hip or knee-joint affected with tuberculosis is put absolutely at rest, and the frequency of cure makes it practically certain that the rest had a definite effect. The treatment of laryngeal tuberculosis by vocal rest is in the same category. The artificial-pneumothorax treatment of tuberculosis of the lungs is likewise postulated on it. If rest of a part, or the restriction of its activity, is in general, and even in the lungs, one of the best means of curing tuberculosis, we cannot also say that it is one of the best means for stimulating development. The statement commonly made that tuberculosis occurs by preference at the apex on account of its limited motion, therefore, falls to the ground. This therapeutic argument pointing toward the greater activity at the apex is so strong as to be almost convincing by itself.

[1] From the Laboratory of Postmortem Pathology of the Philadelphia General Hospital.

2: Bacteriology: A second argument not infrequently stated is that the diminished aeration of the apex, produced by its lessened activity, favors the development of tubercle bacilli. This argument is contradicted by their growth on artificial media, and by the occurrence of tuberculosis throughout the body generally. Tubercle bacilli are aerobic, not anaerobic. On artificial media they grow with predilection on the surface, so that even when planted in the interior, they come to the surface for development. In addition, nature's method of cure is by cutting off the blood supply to the part and throwing an impenetrable wall about the lesion, thus preventing the easy ingress of oxygen. In large purulent collections in the pleura, hip-joint and vertebral column, tubercle bacilli are few, having apparently died due to the lack of oxygen. The fact that bacteria develop better at the apex than elsewhere in the lung would surely therefore prove not less aeration of the part.

3: Physical signs: The circumstance, which led me originally to question the lessened activity of the apex in comparison with other parts of the lung, is the enormous distention, or even ballooning of the apex sometimes seen in attacks of asthma, in which a protrusion of the apex 1 to 3 cm. above its usual situation is not uncommon. In emphysema, the physical signs, the X-ray plate, and the necrospy, all show the alveoli at the apex to be more distended than elsewhere. It is particularly at the apex that we find the alveoli, at postmortem, broken into one another in such numbers that they look like small bladders. In addition, on the X-ray plate of emphysema, the apex frequently looks like a large cavity, the walls of the alveoli being so tenuous as to be invisible. If in emphysema the alveoli at the apex are first to distend, and even rupture into one another the evidence is very great that it is because they are the most active, or have the greatest opportunity to distend or overfunctionate.

4: Macroscopic anatomy: Anatomic study shows the lung surrounded by a bony cage and transverse muscle fibres except at the apex and the mediastinal border. At the apex, the lung expands upward between vertically placed muscles in such a fashion that the possibility of local expansion is very great. At the mediastinal border the local expansion is limited only by the other lung, since we find the margin of the two lungs frequently in contact, even in their partially deflated postmortem condition.

On first thought it would appear that the area of lung tissue between the ribs might distend in a more or less corresponding fashion. Further

consideration, however, shows that on account of the movement of the chest-wall on the lung, there is no place where the lung is sufficiently stationary to protrude between the ribs, and inspection shows that while the space above the clavicle expands on inspiration the costal interspaces are drawn in.

With these thoughts in mind we would expect greatest expansion of the alveoli at the apex and mediastinal border, and the microscopic study of the alveoli apparently shows this to be true.

5: Microscopic study of alveoli: Microscopic study of various parts of the lung fixed in an inflated condition demonstrates the alveoli throughout a child's lung to be of practically the same size, while in an adult's lung they are distinctly largest at the apex. The natural explanation of this overenlargement is overfunction in comparison with other parts of the lung.

In this study, which was suggested by Dr. Joseph Sailer in 1920. and made at the Philadelphia General Hospital that year, and repeated in 1923, normal lungs were half inflated, then filled with 5 per cent formalin and then further inflated to what appeared to be full inspiration. The lung was then hung either in 5 per cent formalin solution, or in an air-tight jar containing about an inch of pure formalin. After two days the lung was found sufficiently hardened in this condition of distention to cut sections from various parts without collapse. Microscopic stained specimens from sections at the apex of the upper and lower lobes, both sides, bases and interior portions of the lungs, showed the alveoli throughout the child's lung to be practically of the same size, and throughout the adult's lung to be largest at the apex, and second largest at the mediastinal border.

I make this statement, knowing that some authorities, like Waters (1), in his excellent monograph on the anatomy of the human lung in 1860, definitely declare that the alveoli in the same lung are practically all of the same size. *Gray's Anatomy* (Lea Brothers, 1887, p. 937) favors somewhat my own investigations, in that it states that the alveoli "are largest on the surface at the three borders and at the apex, and are smallest in the interior."

After noticing the marked difference in size microscopically between the alveoli at the apex and in other situations in the adult lung, I began to study the lungs macroscopically just as they are removed from the body, and found that the larger size of the alveoli at the apex was demonstrable even macroscopically. This macroscopic demonstration is more evident when the lungs do not spontaneously collapse, and is especially evident

in cases of emphysema, even compensatory emphysema. The accompanying microphotographs (figs. 1 to 6) demonstrate the great difference in size of the alveoli so evidently that it is not surprising to learn that this difference can be shown macroscopically.

6: Physics: On blowing air into a distensible bag, it is the upper part which is first inflated, because air naturally ascends. On inspiration, therefore, it is the top of the lung which is first inflated and suffers continuously throughout inspiration the greatest pressure. It probably bears some pressure even on expiration, because on compression of the ribs and diaphragm the air rushes upward, forcing the air in the upper part of the lung back, at least during the first part of expiration. Adding to this physical fact of greatest air pressure at the apex the anatomic fact previously shown, that the alveoli at the apex have the greatest opportunity to expand because they are not restricted by transverse muscles but distend up between vertical muscles, and it is evident that these alveoli will be the first to show signs of over-work.

Conclusion: I contend, therefore, that one reason for the development of tuberculosis at the apices more frequently is their greater activity over other parts of the lungs. Even when the bacilli are distributed uniformly through the lungs, as they are in infection by the circulatory route, they are more likely to develop at the apex than elsewhere. From the physical point of view the alveoli which ought to inflate the least, because they are situated lowest in the distensible lung bag, namely, those at the base posteriorly, occupy the situation in which, according to Tendeloo (2), and my own investigations, tubercles are least frequently found at necropsy. Even in general miliary tuberculosis, almost surely hematogenous in origin, when the patient lives long enough for the tubercles to grow to macroscopic size the tubercles are found to be smaller the nearer they are to the base. In other words, though the opportunity for hematogenous tubercle is equal in all parts of the lung the opportunity for growth is, as we would expect, proportionate to the respiratory activity of the part.

Hanau (3) states that the upper lobes inspire well but expire badly, and on this account particles taken in find a better opportunity to remain in the upper lobes. This seems to me definitely evident, for the two reasons of greater suction at the apex on account of the larger alveoli, and the natural ascent of air by gravity. In addition, expiration forces the air from the lower half of the lung with greater violence than from the upper, so that particles floating out in the air from the lower may still ascend to the upper.

2. THE PHYSICAL CONFORMATION OF THE BRONCHIAL TUBES ALLOWING TUBERCLE BACILLI TO REACH THE APICES, ESPECIALLY THE RIGHT APEX, MORE READILY THAN OTHER PARTS OF THE LUNGS

The respiratory tract has been arranged by nature with the idea of preventing particles, organic or inorganic, from reaching the alveoli. The defenses are of three kinds, a special mucous membrane, a labyrinthine passageway, and residual air. The mucous membrane has two capabilities: first, a thick moisture capable of catching and holding small particles in such a way that, once caught, there is no likelihood of them being carried further; and second, a ciliated epithelium with a special capability of expelling them. This cilated epithelium extends in the tubules until they reach a size of 0.5 mm.

The second defense is a labyrinthine passageway of great complexity, so that the air changes direction seven to ten times before reaching the end of the ciliated epithelium. On account of the ramifications in the nose, an upward, backward and downward movement being necessary to pass through it, the very great majority of inhaled particles are caught on its mucous membrane. In the passage from the nose to the larynx there is a backward, downward and then forward movement. Entering the larynx by a forward motion this changes suddenly to downward. Now is met the obstacle of the vocal cords cutting off half or three-quarters of the diameter of the tube, so that of the particles which start downward through the larynx more than 50 per cent would be interfered with. At the bifurcation of the trachea only the particles in the middle of the current miss striking the mucous membrane, and at the entrance to the lung we have the further bifurcations producing the same effect.

As the air enters the bifurcation of the bronchus, gravity would attract the solid particles toward the lower-lobe branch, except for the same gravity forcing the air to rise, making the current sufficiently greater toward the upper lobe to more than compensate for the action of gravity on these extremely minute particles.

In addition to the natural tendency for air to ascend, making the upward current swifter, we have already demonstrated that the alveoli at the apex distend more than the alveoli in other parts of the lung, making the local suction in this direction even greater than elsewhere, thereby increasing the natural velocity of the current. In the third place, the bronchial branch extending to the apex, namely, the para-vertebral bronchus, is straight, and in the upright or standing position

is almost exactly vertical, so that particles in the centre of the current in their ascent are carried upward without any special tendency to touch the walls; while particles carried into the lower-lobe bronchus, which is at an angle of about 45°, will have a greater tendency to strike the wall and adhere. According to Tendeloo (2) the common situation of primary foci is the immediate vicinity of this paravertebral bronchus. Fourth, there is a special feature in connection with the lower-lobe bronchus, which does not exist in the upper, namely, the beating of the heart. It is evident that every heart-beat partly closes and partly changes the direction of the lower-lobe bronchus for the interval of the beat. There are two beats to every inspiration, and, for the instants of time of these beats, the lower-lobe bronchus is partially closed or deviated. During the time of this closure or deviation a definite percentage of particles is forced to the wall, which would not be interfered with in the upper-lobe bronchus.

The right lung, being about one-ninth larger than the left, uses a correspondingly greater amount of air, which accounts for a correspondingly greater number of particles entering it. Second, because it does attract more air, the current to the right is swifter than to the left, which would mean greater capability of carrying particles without their subsidence to the sides. Third, the bronchial branch to the right-upper lobe, namely, the eparterial bronchus is the highest of the five large bronchi entering the different lobes, and, with the natural tendency of air to ascend, this is the branch exercising the greatest suction.

The third defense is residual air. It is well-known, though frequently forgotten, that expiration does not empty the lung of air; in fact the residual air is six times greater (3000 cc. to 500 cc.) than any ordinary inspiration or expiration. Consequently, when we inspire, we do not draw the external air directly into the alveoli, but instead compress the air already in the lung back into the alveoli, and the new air reaches the alveoli not directly but by diffusion. This diffusion sets up currents in the bronchial tubes, making the possibility of solid particles being caught on the walls still greater, so that they may be expelled by the ciliated epithelium.

The number of particles, whether organic or inorganic, reaching the intralobular respiratory parenchyma is, therefore, infinitesimally small in comparison with the number inhaled into the anterior nares, but of these particles more will reach the lobules at the apex than elsewhere. Various experiments and investigations appear to prove this. For

instance, at General Hospital No. 17 (4) we had guinea pigs inhale barium sulphate by means of a bag about their snout, while they were in the act of being killed, and were making forcible respirations due to their excitement. These lungs showed by X-ray that the barium sulphate accumulated very much more at the apices than at the bases.

To recapitulate: Therefore, on account of the special mucous membrane with its moisture and ciliated epithelium, the labyrinthine passageway, and the residual air, it is extremely difficult for particles to reach the termini of the respiratory parenchyma, but the possibilities of reaching them at the apex are greater than elsewhere, on account of the naturally greater pressure or velocity of air upward, the greater suction of the more active alveoli, the straightness of the paravertebral bronchus, and the failure of the heart-beat interference in the upper lobe; and the possibilities of reaching the right lung are greater than the left on account of the suction being greater, due to its larger size, and the fact that the upper-lobe bronchus is the highest one of the large bronchial branches, giving its current of air the greatest pressure and velocity. The right apex is the first part of the lung to be inflated on inspiration, and the last to be deflated on expiration.

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(2) TENDELOO: On the channels of infection in pulmonary tuberculosis, Tr. Sixth Internat. Congress on Tuberculosis, 1909, i, 86.
(3) HANAU: Quoted by Tendeloo in Studien über die Ursachen der Lungenkrankheiten, Wiesbaden 1902, p. 344.
(4) WALSH, WOOD AND THOMPSON: X-ray study of advanced tuberculosis of the lungs with autopsies, Tr. Fifteenth Annual Meeting Nat. Tuberc. Assoc., June, 1919.

EXPLANATION OF FIGURES

Microphotographs of specimens from different parts of healthy lungs hardened in an inflated conditon (as described on page 179) from a stillborn, full-term infant, and a female adult aged 29, showing the alveoli in the different parts of the baby's lung to be practically similar in size, and in the adult lung to be distinctly larger at the apex. All photographs were taken by Mr. H. H. Gosner under the same magnification.

FIG. 1. (Philadelphia General Hospital) SECTION OF MID-APEX OF LUNG OF STILLBORN, FULL-TERM BABY INFLATED AS DESCRIBED ON PAGE 179.

Notice that the alveoli in the different sections of the baby's lung are practically similar as to size

FIG. 2. (Philadelphia General Hospital) MID-LOWER MARGIN UPPER LOBE ANTERIORLY OF STILLBORN, FULL-TERM BABY

FIG. 3. (Philadelphia General Hospital) CENTRAL INTERIOR PORTION OF LOWER LOBE OF STILLBORN, FULL-TERM BABY

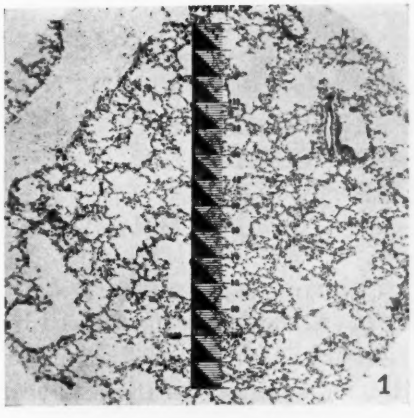
FIG. 4. (Philadelphia General Hospital) EXTREME APEX OF LUNG OF ADULT FEMALE AGED 29

Notice that the alveoli are larger than in the other specimens from other parts of this adult lung. All other sections from this apical area show the alveoli equally large.

FIG. 5. (Philadelphia General Hospital) LOWER MARGIN UPPER LOBE ANTERIORLY OF ADULT FEMALE

The photograph shows the part of the specimen where the alveoli are largest and yet even here they are distinctly smaller than at the apex (fig. 4).

FIG. 6. (Philadelphia General Hospital) CENTRAL INTERIOR PORTION OF UPPER LOBE OF ADULT FEMALE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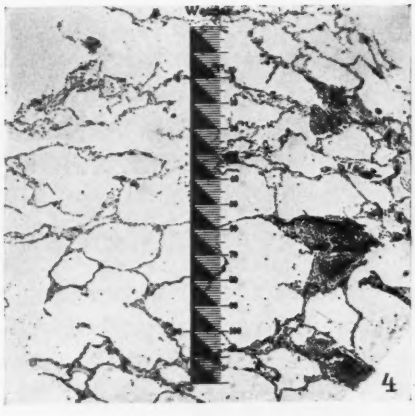
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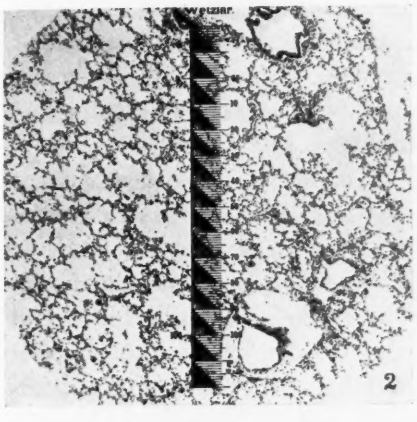
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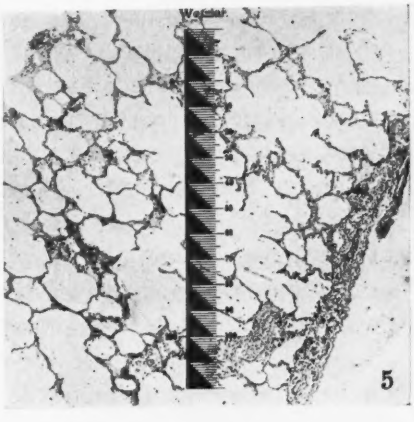
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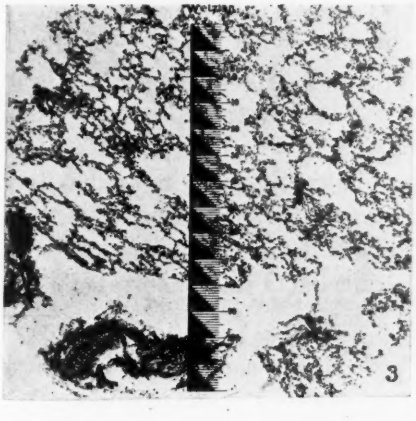
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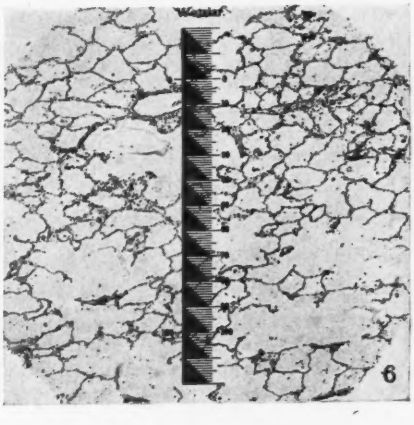

6

TUBERCULOSIS MORTALITY IN RELATION TO THE PASTEURIZATION OF MUNICIPAL MILK SUPPLIES[1]

C.-E. A. WINSLOW AND CORA E. GRAY[2]

The practice of pasteurizing municipal milk supplies has steadily grown in favor during the past twenty years and has been enforced by ordinance in many of the larger cities of the country. The object of pasteurization has been a threefold one: (1) to reduce the diarrheal diseases of infants, (2) to control epidemics of typhoid fever, scarlet fever, septic sore throat and other communicable diseases of human origin, and (3) to guard against the dissemination of bovine tuberculosis.

The reduction in infant diarrhea, and in such milk-borne diseases as typhoid fever and septic sore throat, which has been attained in recent years is obvious and striking, although in both cases the results are due to diverse factors. The decline in the diarrheal death-rate of infants has no doubt resulted chiefly from the general educational work of the infant-welfare station, with its emphasis on breast-feeding and other essentials of infant hygiene, while the acute communicable diseases have been attacked along many different lines. The third problem, that of bovine tuberculosis, is relatively a simpler one, and it seemed to us that it would be of interest to see whether the practice of pasteurization has demonstrably affected mortality from this cause in the cities where it has been put in force. We have assumed that the nonpulmonary tuberculosis of infants and young children should furnish a helpful measure of the extent to which infection from bovine sources has been controlled, since it is generally assumed that disease of this type is due in a substantial proportion of cases to bovine bacilli. We have therefore sought in the present study to compare the reduction in nonpulmonary tuberculosis of infants and young children with the reduction in pulmonary tuberculosis at these same age-periods, as well as in adult life, in cities which have, and have not, affected a reasonably complete pasteurization of their general milk supplies.

[1] Portion of a thesis presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Yale University.

[2] Department of Public Health, Yale School of Medicine.

SOURCES OF DATA

After careful consideration of possible sources of data, 22 cities were selected for the purpose of this study on the basis of available vital statistics running back to 1901 and of reasonably definite information in regard to the extent of pasteurization practised in the respective communities. For the latter point our primary information was derived from Hiscock's paper on *Milk Inspection*,[3] and all cities of over 100,000 population which by 1920 reported 90 per cent or more of their milk supply pasteurized and which were included in the Registration Area in 1900 were included. These cities were 18 in number and comprised all United States cities of over 500,000 population except Los Angeles (Baltimore, Boston, Buffalo, Chicago, Cleveland, Detroit, New York, Philadelphia, Pittsburgh and San Francisco), 6 of the cities between 250,000 and 500,000 population (Cincinnati, St. Louis, Indianapolis, Jersey City, Milwaukee, Minneapolis and Washington), and one smaller city (Toledo). For a control group we selected the 4 largest cities in the Registration Area of 1900 which had 50 per cent or less of their milk pasteurized in 1920 (Denver, New Haven, Providence and Rochester).

By correspondence with the health officers of these 22 cities we obtained the date of the first pasteurization ordinance and the date at which they believed that pasteurization had been developed to such a point that 90 per cent of the milk supply of their respective cities was protected in this fashion. On this basis our cities were divided into four major groups as follows:

Group I: Less than 50 per cent of milk supply pasteurized in 1920: Denver, New Haven, Providence and Rochester.

Group II: Ninety per cent of milk supply pasteurized soon after 1920: Boston, Minneapolis, Pittsburgh, St. Louis and Toledo.

Group III: Ninety per cent of milk supply pasteurized between 1915 and 1920: Baltimore, Buffalo, Chicago, Cincinnati, Cleveland, Indianapolis, Jersey City, Milwaukee and Philadelphia.

Group IV: Ninety per cent of milk supply pasteurized before 1915: Detroit, New York, San Francisco and Washington.

We thus have, at one extreme, cities in which less than half of the milk supply was being pasteurized in the period 1916–1920 (group I)

[3] *Amer. Jour. Public Health, July, 1922.*

and at the other extreme cities in which at least nine-tenths of the milk supply was being pasteurized during the whole of this period (group IV). Groups II and III occupy an intermediate position, having a rapidly increasing application of pasteurization during the period in question. In none of these cities was pasteurization practised to any appreciable degree in 1901–1905. By comparing the two periods 1901–1905 and 1916–1920 in the four groups of cities it should therefore be possible to obtain some measure of the influence of pasteurization upon mortality from tuberculosis.

Our statistical data were all taken from the *Reports of the U. S. Census Bureau.*

As a measure of that portion of the tuberculosis mortality which might presumably be affected by the pasteurization of municipal milk supplies we selected (*a*) nonpulmonary tuberculosis under 1 year of age and (*b*) nonpulmonary tuberculosis at ages 1 to 4. For a control, giving some measure of the general decline in the tuberculosis mortality, presumably not materially influenced by milk supply, we selected (*c*) the mortality from all forms of tuberculosis at the age period, 20 to 29. For a further control we used (*d*) pulmonary tuberculosis under 1 year of age and (*e*) pulmonary tuberculosis at the age period, 1 to 4. The deaths for each city at each age period and by each cause were extracted from the annual volumes of *Mortality Statistics* and the populations were computed for each year from the 1900, 1910 and 1920 censuses.[4] Rates for each year were then computed and are plotted in figures 2 to 10. The average figures for deaths and mortality for the crucial periods of 1901–1905 and 1916–1920 are presented in tables 1 and 2.

DISCUSSION OF RESULTS

In discussing the results of our study we will consider first the rate for nonpulmonary tuberculosis under 1 year of age. In most of the cities this rate showed a marked decrease, exceptions being apparent in Rochester (group I), Pittsburgh (group II), and Cleveland, Indianapolis and Milwaukee (group III). It will be noted by reference to the graphs that in many instances the decrease in this rate was remarkably rapid after pasteurization.

[4] These population estimates were not corrected for the month in which the respective censuses were taken, since preliminary computation indicated that this refinement would not affect the significant figures with which we were dealing.

TABLE 1

AVERAGE POPULATIONS AND AVERAGE DEATHS FROM VARIOUS FORMS OF TUBERCULOSIS FOR CERTAIN CITIES AND GROUPS OF CITIES AT CERTAIN AGES FOR 1901-1905 AND 1916-1920

	20 to 29 Years				Under 1 Year						1 to 4 Years					
	Population		Deaths All Forms Tuberculosis		Population		Deaths Non-pulmonary Tuberculosis		Deaths Pulmonary Tuberculosis		Population		Deaths Non-pulmonary Tuberculosis		Deaths Pulmonary Tuberculosis	
	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920	1901-1905	1916-1920
Group I Cities with 50% of the milk pasteurized in 1920.																
Denver	31 009	47 265	255	253	2 616	3 589	9	6	5	5	10 417	14 118	8	12	3	2
New Haven	23 279	28 636	59	59	2 612	3 415	6	8	4	3	9 371	13 677	7	16	4	4
Providence	39 423	42 326	199	82	3 981	4 882	20	11	9	6	14 427	18 239	27	23	10	11
Rochester	35 880	53 245	72	63	3 400	5 040	3	6	1	2	15 111	22 212	4	17	3	3
Total	129 641	171 522	485	417	12 609	16 926	38	31	19	14	47 526	68 246	46	73	20	20
Group II. Cities with 90% of the milk pasteurized soon after 1920																
Boston	126 375	138 805	377	264	12 802	13 775	42	27	24	23	46 468	55 646	71	54	37	28
Minneapolis	51 945	80 082	89	139	4 575	6 507	5	4	2	3	17 648	27 122	8	11	2	5
Pittsburgh	124 270	112 121	234	204	13 684	12 150	18	15	16	15	41 402	49 052	31	42	25	15
St. Louis	129 762	153 543	389	248	11 905	11 418	14	10	9	6	46 041	47 564	19	19	12	15
Toledo	28 455	46 463	69	102	3 014	3 992	3	3	2	3	11 482	17 351	2	8	3	4
Total	460 785	531 014	1 158	957	45 980	47 822	82	62	53	50	163 041	196 715	131	134	77	65
Group III. Cities with 90% of the milk pasteurized between 1915 and 1920																
Baltimore	104 835	158 521	384	323	10 662	13 929	26	13	18	8	40 295	43 952	37	34	28	27
Buffalo	71 846	95 304	156	208	8 574	9 955	9	10	7	6	32 928	40 189	15	22	7	8
Chicago	384 890	528 068	886	971	42 284	50 737	51	35	35	28	159 094	211 980	76	102	52	45
Cincinnati	68 720	75 120	244	211	6 077	6 812	9	8	7	4	25 549	24 412	21	15	11	9
Cleveland	91 445	155 350	163	296	10 218	16 050	5	18	7	9	38 101	67 193	7	29	10	17
Indianapolis	40 247	59 842	119	138	3 300	4 854	3	5	6	3	12 503	19 278	5	11	7	9
Jersey City	45 116	56 778	158	105	5 390	6 462	11	9	4	1	20 888	26 130	13	15	6	2
Milwaukee	61 537	89 976	133	122	7 543	8 790	8	10	7	5	28 487	35 467	10	17	6	5
Philadelphia	278 216	342 688	870	748	29 476	35 045	62	54	29	28	108 191	138 473	76	91	45	42
Total	1 146 852	541 745	3 115	3,122	125 324	151 824	184	161	120	92	465 995	607 101	260	334	172	162
Group IV. Cities with 90% of the milk pasteurized before 1915.																
Detroit	71 669	214 362	126	316	7 722	19 902	8	18	6	12	28 653	78 735	9	43	5	16
New York	812 071	103 465	2 334	2 078	93 775	109 231	258	156	69	67	336 449	440 880	388	344	162	105
San Francisco	80 764	99 374	281	175	5 650	6 481	22	10	9	4	21 304	25 371	48	30	16	8
Washington	63 746	94 749	259	182	4 977	6 366	11	4	17	3	19 228	23 316	20	15	24	8
Total	1 028 250	511 948	3 000	2 747	112 124	141 980	299	188	92	86	405 634	568 300	465	432	147	137
All Cities	2 765 528	756 229	7 756	7 243	294 057	358 552	603	127	285	242	1 079 995	1 440 362	901	943	416	384

TABLE 2

AVERAGE DEATH RATES PER 100,000 POPULATION FROM VARIOUS FORMS OF TUBERCULOSIS FOR CERTAIN CITIES AND GROUPS OF CITIES AT CERTAIN AGE PERIODS FOR 1901-1905 AND 1916-1920

	All Forms Tuberculosis 20 to 29 Years			Non-pulmonary Tuberculosis under 1 Year			Pulmonary Tuberculosis under 1 Year			Non-pulmonary Tuberculosis 1 to 4 Years			Pulmonary Tuberculosis 1 to 4 Years		
	1901-1905	1916-1920	% Change	1901-1905	1916-1920	% Change	1901-1905	1916-1920	% Change	1901-1905	1916-1920	%Change	1901-1905	1916-1920	% Change
Group I. Cities with 50% of the milk pasteurized in 1920															
Denver	750	495	-34	329	173	-47	184	78	-58	73	85	+16	27	11	-59
New Haven	253	136	-46	246	225	- 9	153	76	-50	70	117	+67	41	29	-29
Providence	302	194	-36	507	221	-56	226	119	-47	181	155	-14	68	58	-15
Rochester	201	119	-41	100	127	+27	24	48	+80	33	78	+137	23	14	-39
Total	373	243	-35	306	185	-40	147	80	-46	96	107	+13	41	28	-32
Group II. Cities with 90% of the milk pasteurized soon after 1920.															
Boston	298	190	-36	328	196	-40	187	169	-10	154	98	-36	79	51	-35
Minneapolis	171	174	+ 2	109	68	-38	48	49	+ 2	45	41	- 9	10	18	+18
Pittsburgh	188	110	-42	130	152	+17	118	125	+ 6	75	87	+16	56	31	-45
St. Louis	300	162	-46	119	84	-29	79	56	-29	41	40	- 2	27	27	0
Toledo	242	219	-10	95	75	-19	67	80	+19	19	45	+137	23	34	+48
Total	251	180	-28	178	130	-26	117	107	- 8	81	68	-16	49	33	-33
Group III. Cities with 90% of the milk pasteurized between 1915 and 1920															
Baltimore	369	234	-37	247	92	-63	169	56	-67	92	77	-16	70	62	-11
Buffalo	217	218	0	107	105	- 2	84	58	-31	44	55	+25	20	19	- 5
Chicago	230	185	-20	121	69	-43	85	55	-34	48	48	0	33	20	-39
Cincinnati	355	281	-21	155	130	-16	42	67	+59	90	61	-32	49	36	-26
Cleveland	178	191	+ 7	53	111	+79	67	59	-12	18	43	+139	26	26	0
Indianapolis	296	230	-22	85	95	+11	170	58	-66	58	55	+45	59	45	-24
Jersey City	350	185	-47	202	141	-30	82	19	-77	62	51	-18	28	77	+175
Milwaukee	216	136	-37	104	109	+ 5	98	52	-47	34	49	+44	21	15	-29
Philadelphia	313	217	-31	207	154	-26	99	89	-10	70	66	- 6	41	30	-27
Total	272	205	-25	149	106	-31	97	65	-33	56	55	- 2	37	27	-27
Group IV. Cities with 90% of the milk pasteurized before 1915.															
Detroit	176	147	-17	101	88	-13	78	58	-26	31	55	+77	19	20	+ 5
New York	288	188	-35	275	143	-48	64	61	- 5	115	78	-32	30	24	-20
San Francisco	348	174	-50	388	155	-60	166	59	-65	226	118	-48	77	33	-57
Washington	407	192	-53	221	65	-71	342	50	-85	105	63	-39	127	36	-72
Total	292	182	-38	266	133	-50	82	60	-27	115	76	-34	37	24	-35
All Cities.	280	193	-31	204	127	-38	97	69	-29	83	68	-18	39	27	-31

The actual rate varies enormously in different cities, from 65 in Washington in 1916–1920 to 507 in Providence in 1901–1905. Evidently, local conditions, and perhaps factors of diagnosis, materially affect the statistics. The more extreme variations are however eliminated by using the rates for the four groups of cities, each group taken as a whole. These rates and the reductions effected, when one compares 1901–1905 with 1916–1920, are indicated in table 3.

The original rates were highest in groups I and IV, and these two groups show the most marked reductions. The fact that the rates in the cities of group I, with little pasteurization, have fallen nearly as rapidly

TABLE 3

Mortality from nonpulmonary tuberculosis under 1 year

	1901–1905	1916–1920	PER CENT REDUCTION
Group I	306	183	40
Group II	178	130	26
Group III	149	106	31
Group IV	266	133	50
All cities	204	127	38

TABLE 4

Mortality from pulmonary tuberculosis under 1 year

	1901–1905	1916–1920	PER CENT REDUCTION
Group I	147	80	46
Group II	117	107	8
Group III	97	65	33
Group IV	82	60	27
All cities	97	69	29

as those of group IV, with almost complete pasteurization, throws serious doubt on any assumed relation to general municipal milk supply.

In table 4 are presented the data for pulmonary tuberculosis in infancy.

It appears from a comparison of tables 3 and 4 that in infancy nonpulmonary tuberculosis has decreased less than pulmonary tuberculosis in the cities without pasteurization, while in two of the pasteurizing groups (II and IV) nonpulmonary tuberculosis has decreased faster than that of pulmonary origin. In the three groups of pasteurizing cities, however, there is no clear relation to the length of time for which pasteurization has been practised, group III showing a greater reduction in the pulmonary than in the nonpulmonary type. The suspicion that

commercial pasteurization of municipal milk supplies has not markedly influenced nonpulmonary tuberculosis of infants is strengthened by comparison with the statistics for adult tuberculosis of all forms, as presented in table 5.

Almost exactly the same relations appear for adult tuberculosis of all types as were manifest for nonpulmonary infant tuberculosis. Both rates were highest in the cities of groups I and IV; both have fallen most rapidly in the cities of groups I and IV; and the relative changes of mortality from tuberculosis at the two age periods are much the same in the four groups of cities. Furthermore, inspection of the graphs makes it clear that the two curves (for nonpulmonary tuberculosis under 1 and for all forms of tuberculosis between 20 and 29 years) exhibit a close parallelism. The graphs for Denver, Boston, Baltimore, Chicago, Philadelphia and Washington are particularly striking in this connection. Where the infant rate has fallen after pasteurization (or without pasteurization) the adult rate has also fallen and vice versa. New York offers the only case, among the pasteurization cities, of a decline in infant tuberculosis markedly more rapid than that manifest among adults. It would appear that nonpulmonary tuberculosis among infants has varied with all forms of tuberculosis among adults, and presumably in response to the same controlling factors; and that it has not been notably affected by the pasteurization of municipal milk supplies. The net decrease in nonpulmonary tuberculosis of infants for all cities is however distinctly greater than that for pulmonary tuberculosis of infants or for all forms of tuberculosis of adults.

TABLE 5

Mortality from all forms of tuberculosis at ages 20 to 29

	1901–1905	1916–1920	PER CENT REDUCTION
Group I	373	243	33
Group II	251	180	28
Group III	272	203	25
Group IV	292	182	38
All cities	280	193	31

Turning now to nonpulmonary tuberculosis at ages 1 to 4 we find a distinctly different picture as indicated in table 6.

In the first place it is evident that the reduction in nonpulmonary tuberculosis at ages 1 to 4 has been very much less marked than in infancy (only 18 per cent for the whole group of 22 cities). In Denver, New

Haven and Rochester (group I), Pittsburgh and Toledo (group II), Buffalo, Cleveland, Indianapolis and Milwaukee (group III), and Detroit (group IV) this rate was higher in 1916–1920 than in 1901–1905.

In the second place, there appears, so far as nonpulmonary tuberculosis is concerned, to be a somewhat significant relation to pasteurization. Of the cities of group I with relatively little pasteurization all but Providence (which was very high at the start) show a marked increase. Of the cities of group IV, with practically complete pasteurization, all but Detroit (which was very low at the start) show a marked decrease. There is at least a strong suggestion in the graphs of a real influence exerted by pasteurization upon tuberculosis mortality at this age period.

TABLE 6

Mortality from nonpulmonary tuberculosis at ages 1 to 4

	1901–1905	1916–1920	PER CENT REDUCTION
Group I	95	107	−13 (increase)
Group II	81	68	16
Group III	56	55	2
Group IV	115	76	34
All cities	83	68	18

TABLE 7

Mortality from pulmonary tuberculosis at ages 1 to 4

	1901–1905	1916–1920	PER CENT REDUCTION
Group I	41	28	32
Group II	49	33	33
Group III	37	27	27
Group IV	37	24	35
All cities	39	27	31

The rates for pulmonary tuberculosis at ages 1 to 4 (table 7) furnish a useful check on this conclusion.

Pulmonary tuberculosis at ages 1 to 4 has shown the decrease of about 30 per cent characteristic of the general decline in this disease at all ages. Taking the 22 cities as a whole, pulmonary tuberculosis between 1901–1905 and 1916–1920 shows a reduction of 29 per cent in infancy, and of 31 per cent between the ages 1 to 4, while all forms of tuberculosis at ages 20 to 29 (almost wholly pulmonary) show a reduction of 31 per cent. On the other hand, nonpulmonary tuberculosis in infancy has fallen more sharply (38 per cent) and nonpulmonary tuberculosis at ages 1 to 4 much less sharply (only 18 per cent).

When we compare the groups of cities, it appears that pulmonary tuberculosis at ages 1 to 4 has decreased by about the same amount in various groups. On the other hand, nonpulmonary tuberculosis has increased by 13 per cent in the cities without pasteurization (group I) and has decreased most markedly (34 per cent) in the cities with most complete pasteurization (group IV). It is true that the cities of group II show a greater reduction than those of group III but this is largely due to the markedly decreased death rate in Boston where pasteurization was considerable before 1916 although the ninety per cent point was not reached till 1921.

Inspection of the graphs shows that at ages 1 to 4 nonpulmonary tuberculosis has remained practically constant for the whole twenty-year period in all four cities of group I. In the cities of group II the rate has remained constant, or increased slightly, except in Boston (where, as pointed out above, pasteurization begun in 1903 had really progressed considerably by 1916). In the cities of group III again we note an actual rise in mortality, or an insignificant fall, except in Cincinnati. Out of the 18 cities of groups I, II and III, only 5 show a reduction of over 10 per cent in the nonpulmonary tuberculosis rate at ages 1 to 4 when we compare 1916–1920 with 1901–1905. The actual reductions for these cities are: Boston, 36 per cent; Cincinnati, 32 per cent; Jersey City, 18 per cent; Baltimore, 16 per cent; Providence, 14 per cent. Four of the 18 cities show a reduction of less than 10 per cent, while the other 9 cities show an increase.

On the other hand, of the 4 cities in group IV only Detroit shows an increase, while New York, San Francisco and Washington all show decreases of over 30 per cent. The data for Detroit are of very doubtful accuracy on account of the enormous population changes which took place during the war period.

SUMMARY AND CONCLUSIONS

1. It appears evident from this study that between the periods 1901–1905 and 1916–1920 the mortality from pulmonary tuberculosis at the age periods under 1 year and 1 to 4 years, as well as the mortality from all forms of tuberculosis (chiefly pulmonary) at ages 20 to 29 years, showed a reasonably uniform decrease of about 30 per cent in the large cities whose statistics have been analyzed.

2. The mortality from nonpulmonary tuberculosis during the first year of life showed, on the whole, a slightly greater decline (38 per cent

for the whole group of cities studied). This decrease has been no greater in those cities with a milk supply which has been generally pasteurized than in the cities where milk has not been so completely protected in this fashion (see fig. 1). We are inclined to attribute the general success thus attained in dealing with nonpulmonary tuberculosis in the first year of life to the general campaign for education in the hygiene of infancy with its vigorous emphasis upon breast-feeding or home pasteurization of milk used for infants.

3. It would appear probable that the death-rate from nonpulmonary tuberculosis of infants in cities which have a thoroughly pasteurized milk supply cannot in any considerable degree be due to bovine infection. It appears, therefore, that infection from human sources alone may account in infants for a nonpulmonary tuberculosis rate of about 130 per 100,000 combined with a pulmonary rate of about 60 per 100,000,—the total mortality from tuberculosis being slightly greater than that which obtains at ages 20 to 29. Bovine infection would seem to-day to be of negligible importance among infants in large cities where the infant-welfare campaign has been vigorously carried on.

4. At the age period from 1 to 4 years, on the other hand, variations in nonpulmonary tuberculosis are strikingly correlated with the extent of commercial pasteurization (fig. 1). The group of cities having less than half their milk supply pasteurized in 1920 show an increase of 13 per cent in mortality from nonpulmonary tuberculosis at this age period. The cities which attained the pasteurization of nine-tenths of their milk supply, either between 1915 and 1920 or shortly after 1920, show a slight reduction. The cities which had reached this degree of pasteurization before 1915 show a 34 per cent reduction in nonpulmonary tuberculosis at this age period. It would thus appear that, from the standpoint of the results attained in the reduction of nonpulmonary tuberculosis at ages 1 to 4, the practice of pasteurization has begun to yield fruits which are susceptible of statistical demonstration.

5. It would appear probable that the death-rate from nonpulmonary tuberculosis of children between 1 and 4 years of age in cities which have a thoroughly pasteurized milk supply is about 75 per 100,000 population, as against a pulmonary rate of about 25 per 100,000. In cities which have not effectively pasteurized their milk supplies the pulmonary rate is about the same, but the nonpulmonary rate rises to about 100 per 100,000. An excess of 25 deaths per 100,000 indicates the approximate danger from bovine tuberculosis at this age period.

Figure 1. Percentage Change in Tuberculosis Mortality by Type and Age according to Degree of Pasteurization between 1901-1905 and 1916-1920.

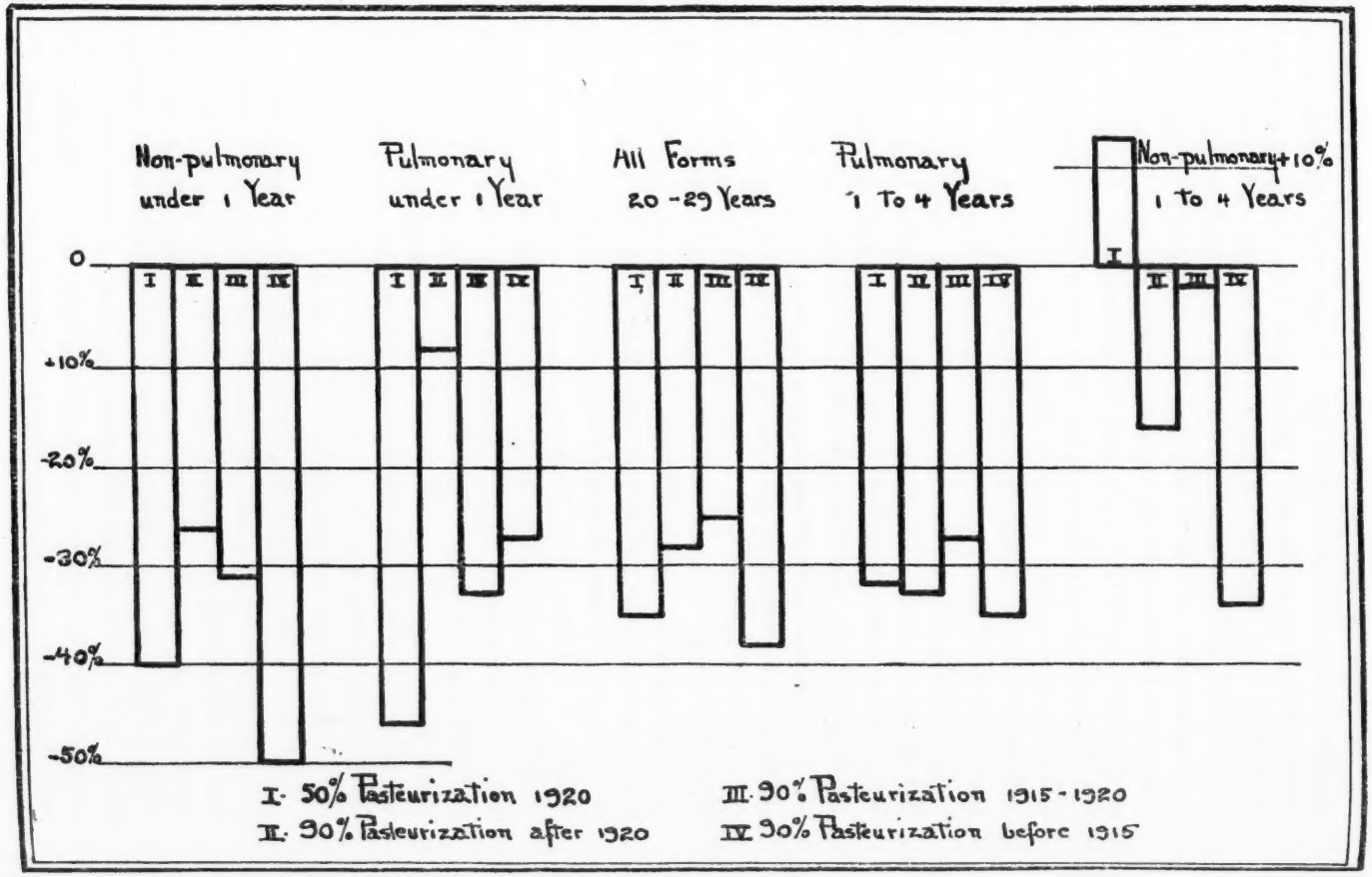


Figure 2. Death Rates per 100,000 Population from Various Forms of Tuberculosis Cities of Group I.

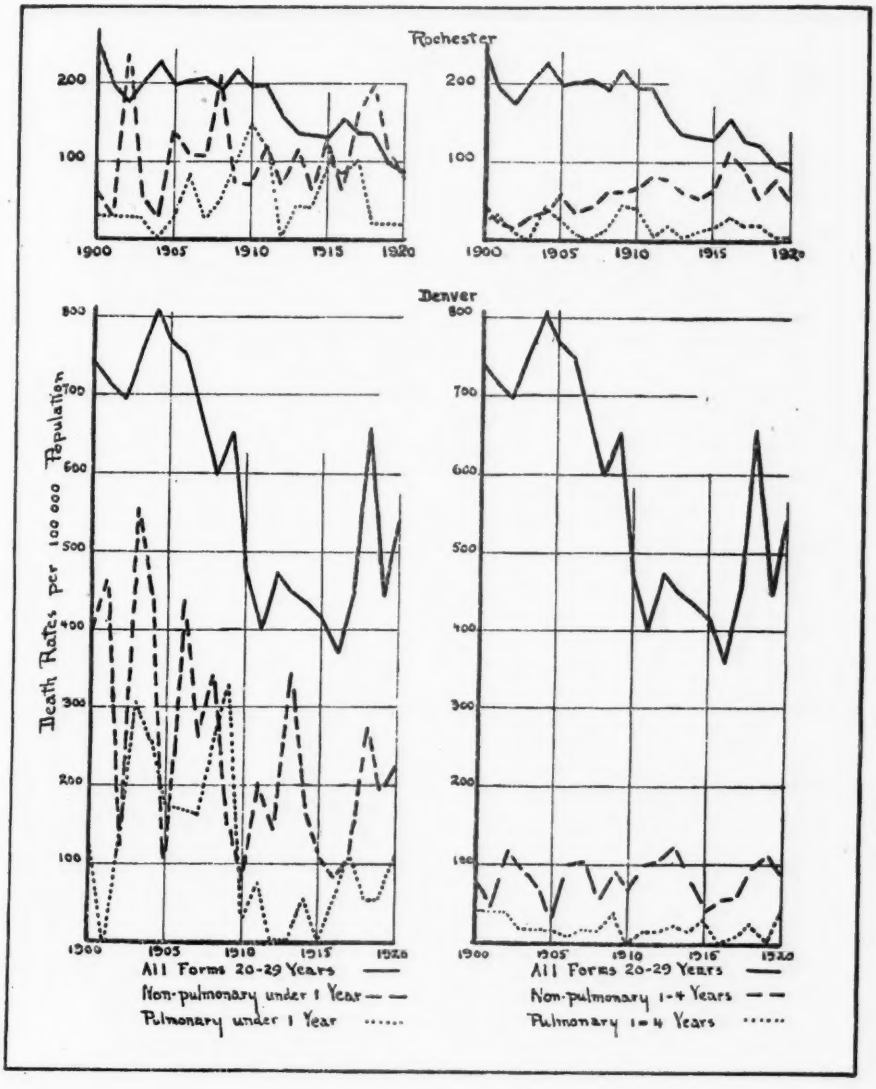


Figure 3 Death Rates per 100,000 Population from Various Forms of Tuberculosis. Cities of Group I.-Continued.

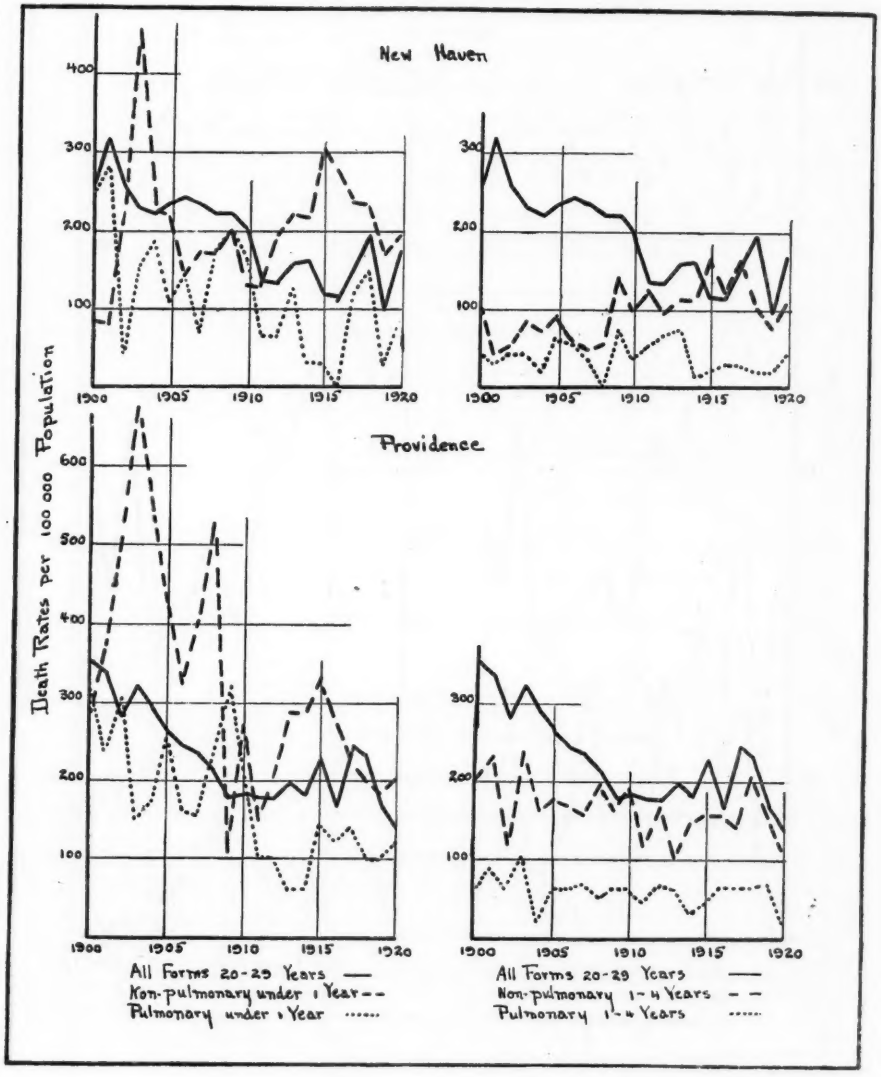


Figure 4. Death Rates per 100,000 Population from Various Forms of Tuberculosis. Cities of Group II

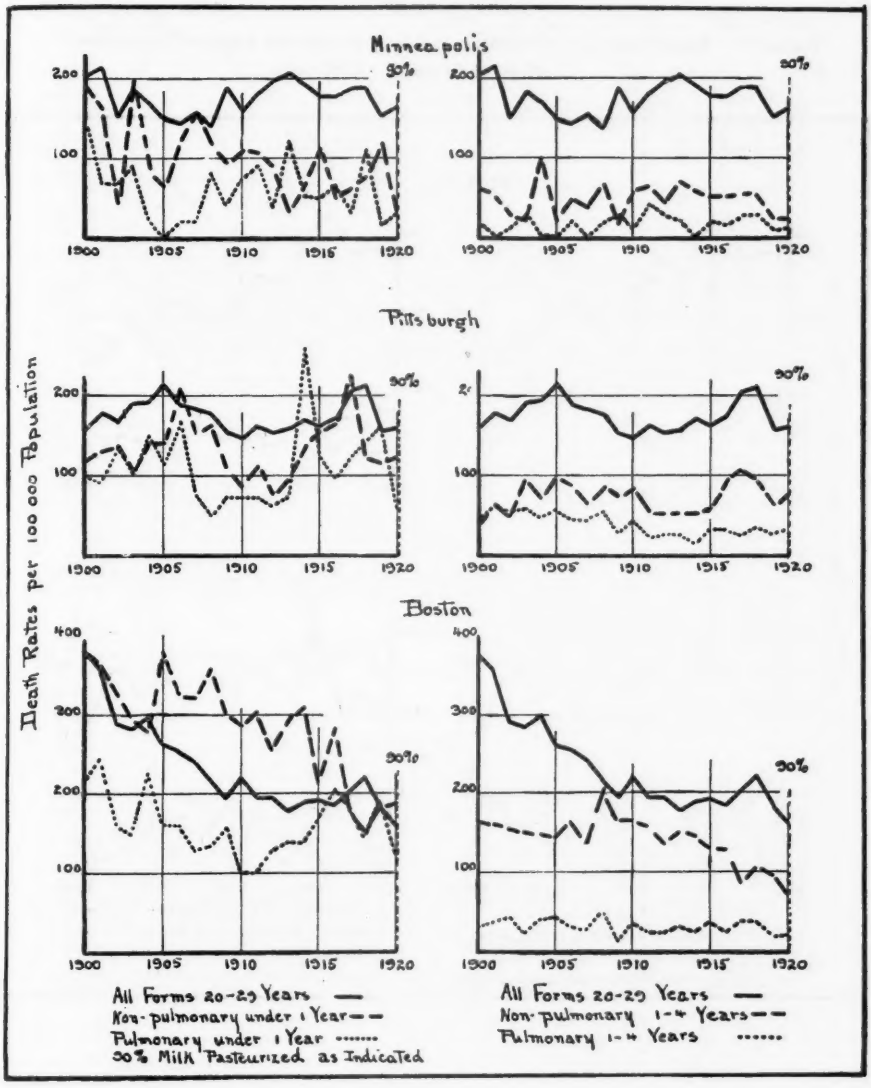


Figure 6. - Death Rates per 100,000 Population from Various Forms of Tuberculosis Cities of Group II- Continued.

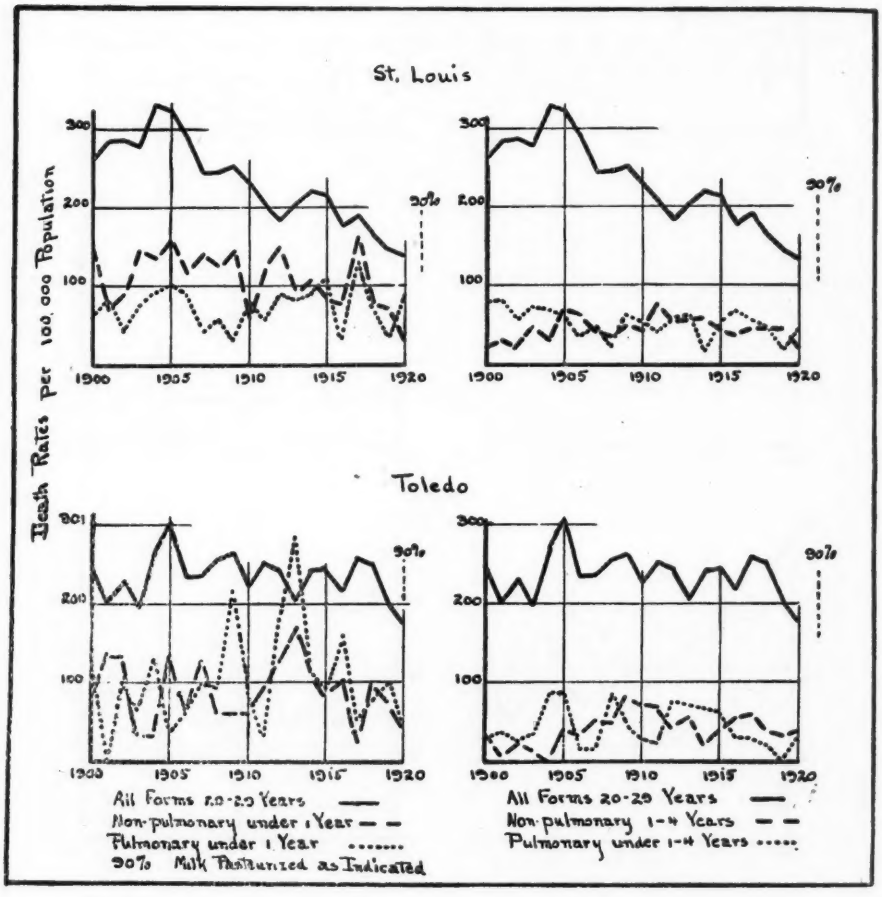


Figure 6 Death Rates per 100,000 Population from Various Forms of Tuberculosis Cities of Group III.

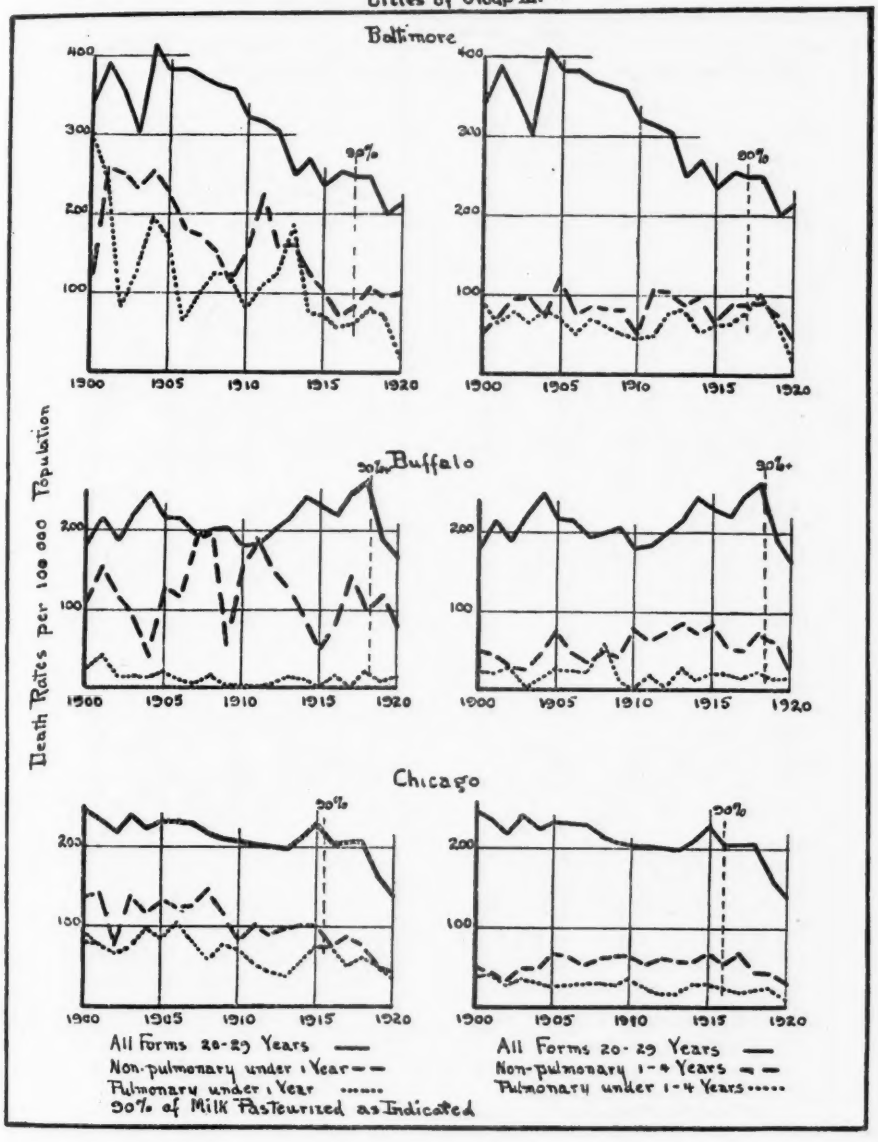


Figure 7. Death Rates per 100,000 Population from Various Forms of Tuberculosis. Cities of Group III – Continued.

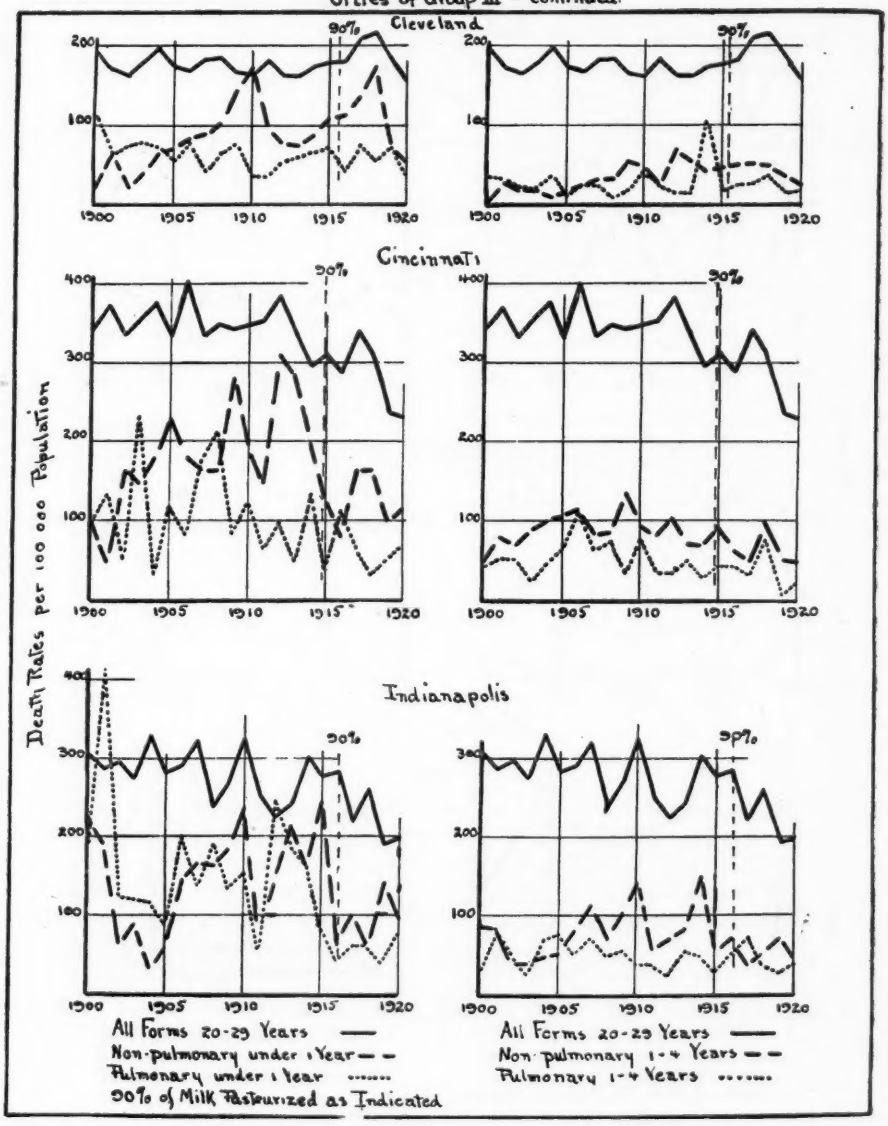


Figure 8. Death Rates per 100 000 Population from Various Forms of Tuberculosis Cities of Group III. Continued.

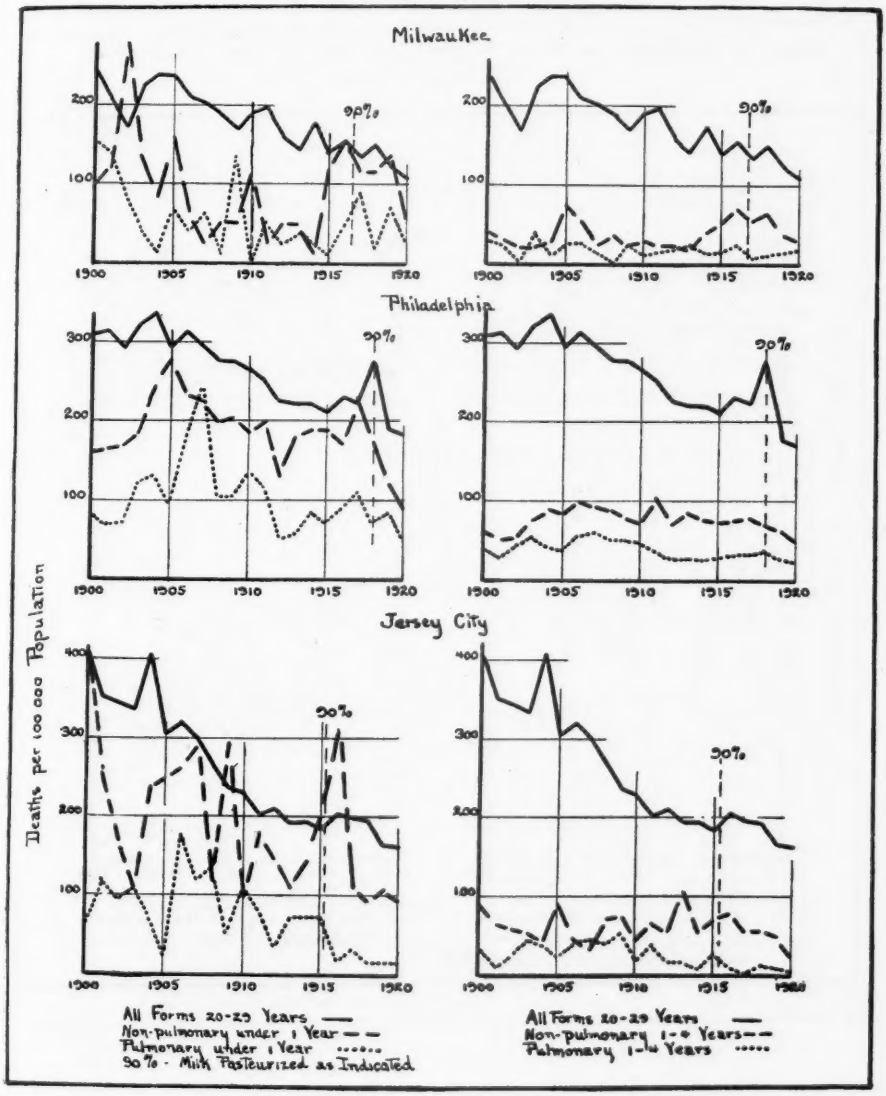


Figure 9. Death Rates per 100,000 Population from Various Forms of Tuberculosis Cities of Group IX

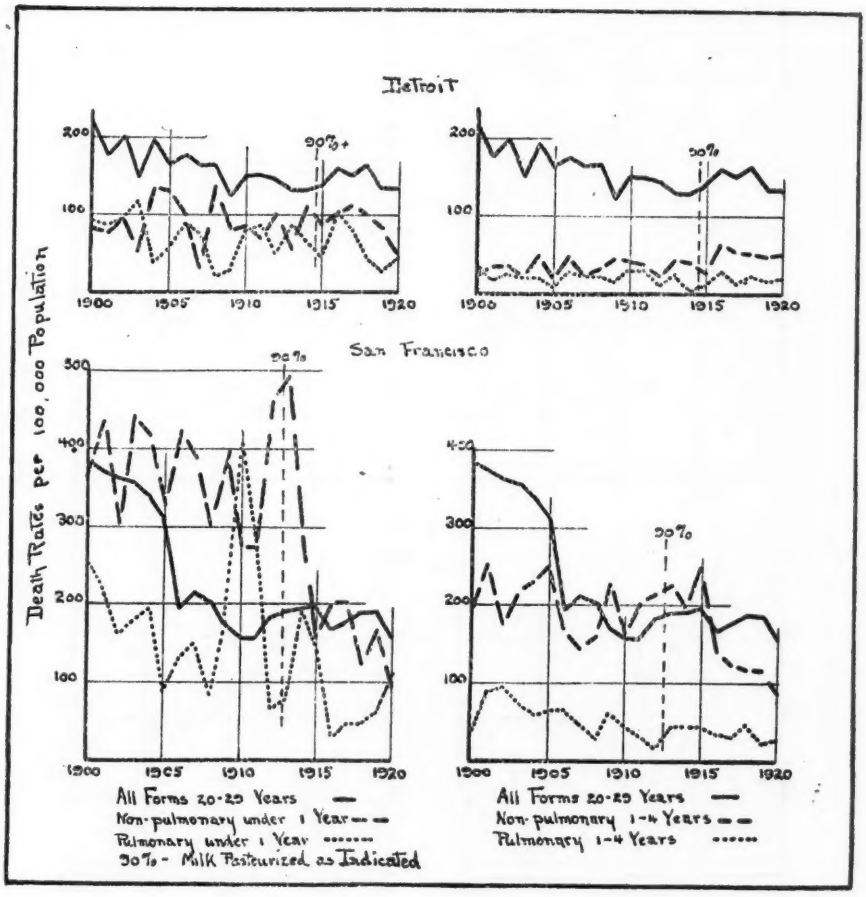
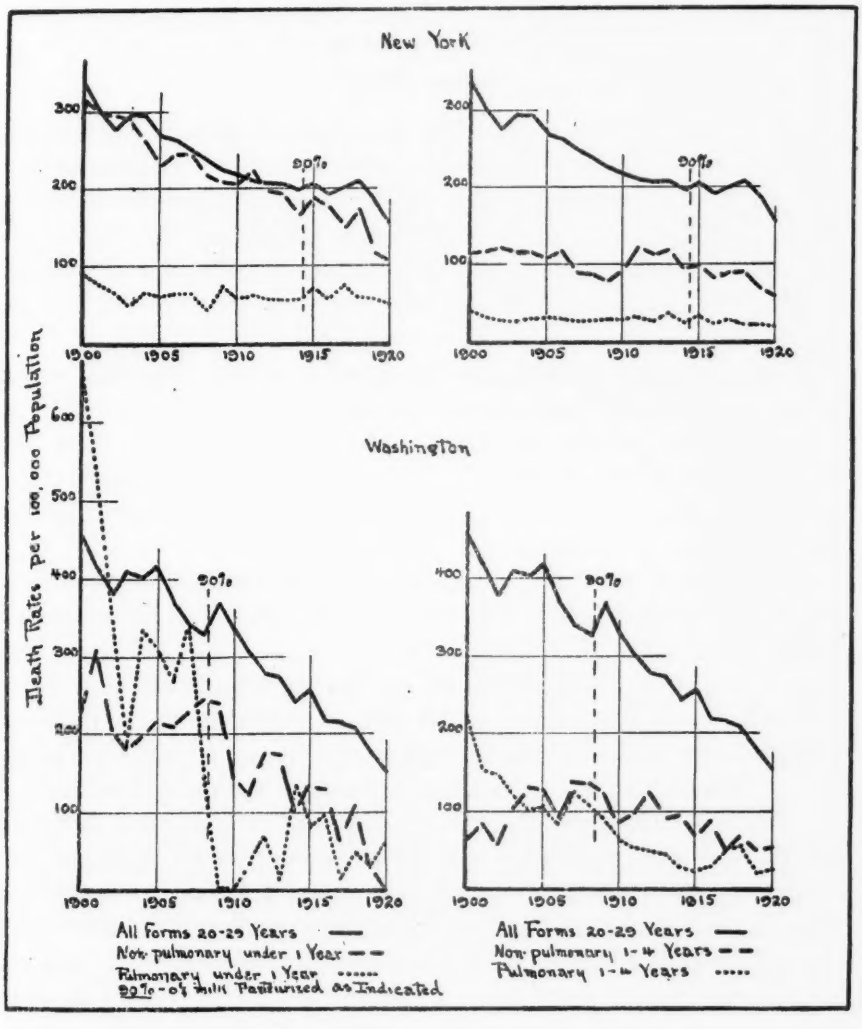


Figure 10. Death Rates per 100,000 Population from Various Forms of Tuberculosis. Cities of Group II - Continued.



A NEW STERILIZER FOR SPUTUM

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During the last thirty years the technique of hospital hygiene has made great strides forward. Many devices to promote the greatest possible asepsis have been invented. It is therefore somewhat surprising that more attention has not been devoted to the destruction of infectious material in sputum and to the conscientious sterilization of sputum glasses, pots and bottles. In this connection there are particular dangers in respect to tuberculous infection.

In sanatoria and the tuberculosis wards of general hospitals, where so much sputum is expectorated and handled, we must care for it in a way that will protect not only the patients but, more especially, the nurses. Since the latter are obliged to minister to the ill throughout the entire day, they may be greatly exposed to infection, and it is our duty to reduce this danger to a minimum.

As Spengler, Cornet and others have shown, chemical disinfectants, which may be used for the disinfection of the faeces and urine, are not altogether suitable for sputum. We cannot, however, entirely avoid chemical methods; as, for instance, in the purification of the remains of sputum in the beds and on tables and other utensils in the patients' surroundings. If we use solutions of lysol or cresol for these purposes, we must take other means to sterilize the sputum and the sputum bottles. For a considerable time, therefore, we have had an apparatus, such as a sterilizer for sputum, like the model for the sterilizer for bandages constructed by Lautenschläger and the apparatus of Tobiesen in Copenhagen which is on the same principle. In both these sterilizers the bottles with sputum are placed in a cylindrical autoclave at different levels, and are then sterilized with steam under a pressure of 1.2 atmospheres absolute and at a temperature of from 102° to 105°C. The disagreeable features of this method are, first, the production of foul-smelling gasses by reason of the high temperature and, second, the emptying and washing of the

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bottles by hand. To avoid the latter drawback, the firm of Haussmann in St. Gallen has, on the design of Philippi of Davos, constructed an apparatus that sterilizes and afterward cleanses mechanically.

Although this apparatus has more good qualities than the others, it nevertheless has some faults which make it unsuitable. It was for this reason that, when charged with the oversight of the greater part of the Tesselschade Hospital for consumptive patients, I attempted to devise an improved apparatus that would unite all the good qualities of the Haussmann sterilizer and would at the same time better satisfy technical and hygienic requirements. With the practical coöperation of Becht and Dyserinck, Nederlandsche Fabriek van Bronswerken at Amsterdam, who have constructed an apparatus according to my plans, I have succeeded in perfecting a sterilizer which fulfills all the requirements mentioned, as well as the prime essential of being so simple that it can be safely and satisfactorily operated by unskilled servants. All bodily movements used in working the sterilizer are those of the most natural acts, while all manoeuvres, such as receiving, cleaning, disinfecting, drying and delivering, are simplified in such a way that the hands never come in contact with infectious material.

The apparatus consists of a rectangular basin, with a double-walled bottom, which is joined to the steam and exhaust pipes (see figures 1 and 2). In the back wall of the basin are perforated nipples, which are connected with a double-walled tank of a solution of sodium, placed high and joined as well to the hot water pipes and the steam exhaust pipes. It is possible to fill the tank with water, so as to get just the proper proportion of sodium; afterward, by opening the steam-cock the temperature can be elevated to boiling.

Through the middle of the basin runs a longitudinal, double-grooved bar. Into these grooves is fitted a set of baskets for the sputum bottles. The bottles are fastened in the baskets by a rectangular hook and the baskets connected to the grooves of the bar with a tumbling clasp-screw. The grooved bar, fitted with basket and sputum bottles, can be rotated by a hand-wheel, placed outside. By turning the wheel 180 degrees the grooves underneath are brought above and a second basket filled with bottles can be inserted.

Each of the two baskets has fourteen compartments for sputum bottles. The entire apparatus has been therefore designed for twenty-eight bottles, in order to be made practicable for use in our hospital where the wards have twenty-eight beds. Of course, the apparatus can be made

of any size, and one that contains sixty bottles is projected for the Dutch Sanatorium at Davos.

The basin of the sterilizer is provided with a cover containing a water-shutter. It is also equipped with a water-gauge glass and a vent in the bottom. Immediately under the basin a cock is placed in the tube of the vent. This cock can be operated with the foot.

The sputum bottles are placed in the basket without any difficulty by the patients. The filled basket is brought to the sterilizer and

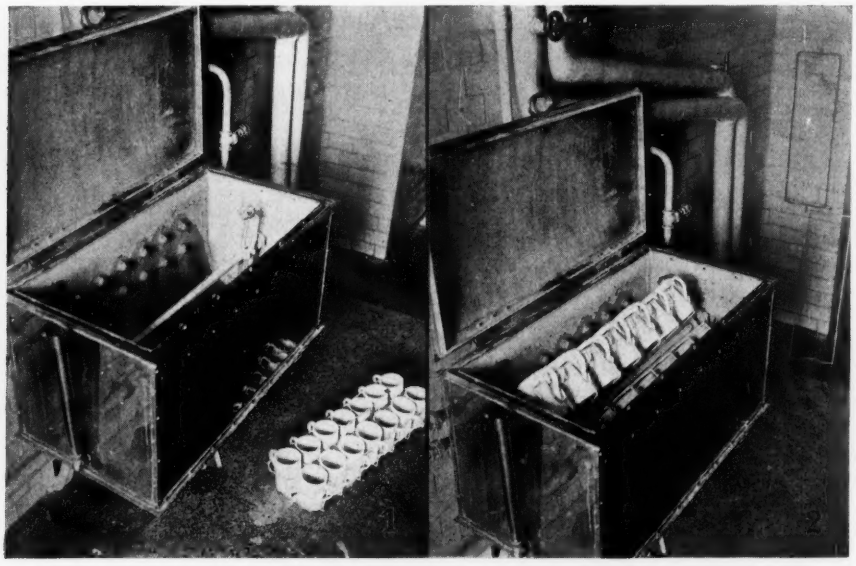


FIG. 1 FIG. 2

FIG. 1. STERILIZER, OPENED TO SHOW INTERIOR, AND BASKET OF SPUTUM CUPS
FIG. 2. STERILIZER, OPENED TO SHOW CUPS IN PLACE AND READY FOR STERILIZATION

fixed into the grooves of the longitudinal bar. The bar is now turned by means of an outside hand-wheel. In this way the bottles are emptied and a second basket can now be attached in the same way.

The cover of the sterilizer is now shut down and the bottles brought to a horizontal position according to a control sign on the hand-wheel outside. This places the bottles of one of the baskets with their insides turned toward the perforated nipples. That cock which communicates with the sodium tank is then opened and the nipples squirt the solution of sodium into the bottles of the first basket. Then the hand-wheel is

turned slowly until the other basket with its bottles has arrived opposite the nipples which now clean the interior of this second set. By turning the hand-wheel slowly a second time or more, both the insides and outsides of the bottles are cleansed of attached material.

Meanwhile, the sputum has collected with the sodium solution at the bottom of the sterilizer. We might sterilize this fluid with steam at a temperature of 100°C. We do not, however, do this, but immediately evacuate it through the exhaust pipe at the bottom of the sterilizer, by opening the cock with the foot, and the fluid is carried away to the sewer. After this evacuation, this cock is shut off; and now the hot water cock is opened and the nipples squirt hot water into the basin of the sterilizer, while at the same time, the sputum bottles are cleaned both inside and out with hot water. The filling of the basin with hot water is controlled by means of the water-gauge glass. After the sputum bottles are completely under water, the hot water is shut off and a steam cock opened to bring the contents to boiling temperature, which is kept up for fifteen minutes, and the bottles are thoroughly sterilized. Then the contents of the sterilizer are drained by turning open the exhaust pipe in the bottom. The hand-wheel is now turned once more, so that the bottles are drained of all fluid, and the sterilizer is then opened. Because of the high temperature to which they have been subjected the bottles dry rapidly and after cooling are again ready for use.

A METHOD OF TEACHING STUDENTS THE DIAGNOSIS OF PULMONARY TUBERCULOSIS[1]

ISADORE KAUFMAN

Of the many phases of the antituberculosis crusade, none is, by general agreement, of more importance than the proper diagnosis of the disease. In order to obtain apparent arrest of pulmonary tuberculosis in any considerable number of cases, it is imperative to begin treatment in the early stage and, unless diagnosis has been made, the patient will often drift until the disease becomes moderately or far advanced. It is obvious that acute miliary tuberculosis is an exception to this rule when it is not superimposed on an earlier localized process.

The University of Pennsylvania endeavors to give its students the opportunity to obtain this instruction at its tuberculosis department, the Henry Phipps Institute. Students of the third-year class are divided into four sections, each of which comes to the Institute one day a week for eight periods. One and a half hours is the time allotted for each period, or a total of twelve hours, in which to give such a course. Previously, my section has consisted of 15 to 17 students, but additional instructors this year have reduced the number of students to 10 or 12. However, I am following the same method of instruction which has apparently yielded results during the past five years.

Using three adjoining rooms, the section is divided into small groups, and I am able to keep in close touch with the work of each student, who is soon made to realize that strict attention to all details is essential for him to obtain benefit from the course. One or more patients, selected from the outpatient department, are studied in each room. The material for each demonstration is gathered with a particular purpose in mind, and each one represents a thoroughly studied patient by the instructor.

The method employed may be described as a building up of a diagnosis step by step and, later, the study of cases as a whole. Each instruction will be described in detail, that you may gather my meaning of the method. Some phases of diagnosis are more easily grasped than others; I therefore begin with changes in the spoken and whispered voice while

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

percussion is considered last. During the first six instructions I am constantly with the students, and every step of their work is closely supervised. A few graduate physicians study in the clinics on other days, and I find the same system of great benefit to them also, although they can advance more rapidly and the lecturing can be omitted by referring them to textbooks.

The first instruction concerns the demonstration of changes in spoken and whispered voice sounds in pulmonary tuberculosis. This is preceded by instruction in the fundamentals of conducting an examination with special reference to proper position of the patient, removal of all clothing to the waist and observance of rigid silence in the room. The spoken voice is compared from side to side, beginning at the bases and proceeding to the apices, and then proceeding from base to apex on either side. I show the students how to handle the stethoscope and the method of proceeding in the examination, noting with a skin-pencil the areas in which changes from the normal are present. As a rule, advanced cases are used, especially those showing but slight changes on one side, which is pointed out as the more important to be studied. After each patient has been demonstrated to the group in that particular room, the subdivisions in each room change about until each student has had the opportunity of eliciting the voice sounds in each of the three patients.

In studying whispered voice sounds the student is shown how quietly the patient must whisper and the differences of intensity of transmission in case of infiltration, consolidation or cavity, whispering pectoriloquy being designated for dense consolidation or cavity. The histories of the three patients are now given to the students in a general group, and it is pointed out to them that the proper taking of a history is most important, especially since the diagnosis of early tuberculosis must frequently be made from history rather than from physical examination, X-ray or other laboratory studies. This is followed by a brief talk on the surface anatomy of the lung, with especial emphasis on the apices, limits of bases and the fissures.

The second meeting of the section is principally occupied with a study of the râles in pulmonary tuberculosis, and I teach that there are two great subdivisions of these adventitious sounds, crackling and whistling. The former are usually heard when produced in the alveoli or pleura, while the latter are produced in the bronchi. They are further subdivided into fine, medium and coarse, the number of râles being indicated by the terms occasional, few, moderate or many. I endeavor to point out

râles in various stages of tuberculosis, showing the coarser râles in the more advanced cases, but of course not omitting the instruction that râles may be absent in a very obvious case of tuberculosis.

Special emphasis is placed on râles which are elicited only with cough, for this is so often the occurrence in cases with scattered infiltration, especially in the apices of the upper lobes. The cough must be properly used to be of value.

Cases with whistling râles are exhibited along with those of the crackling variety, so that the students may know the characteristics of each. It is pointed out to them that whistling râles are usually bilateral and general, occur in both inspiration and expiration, and may disappear after cough. Crackling râles, unless the disease is in the pleura or is massive in the lungs, occur often only with cough and are heard best with the cough or the very beginning of inspiration, are usually localized and rarely disappear with cough. When ulcerative disease is present the râles usually shade off in intensity and number from the apex toward the lower limit of the lesion, although any type of râle may be present in any given case. It is also pointed out that tuberculosis is not infrequently accompanied by a bronchitis and that both general types of râles may be present at the same time.

As in the previous instruction, each student auscultates for râles each of four or five patients, who have been carefully selected for the demonstration, and emphasis is placed on the regions where occasional fine, crackling râles are elicited. Each student is given the opportunity to test one advanced case of tuberculosis for changes in spoken and whispered voice. Then the section is assembled, when the histories of the cases are studied in detail and the complete diagnoses are given.

Following this a brief talk is given on the abrupt onset of pulmonary tuberculosis, with special emphasis on hemoptysis and pleurisy, with or without effusion, as being presumptive evidence of tuberculosis, unless definite causes for the conditions have been discovered. The students are also instructed as to the frequency of fistula-in-ano and ischiorectal abscess without obvious cause being of tuberculous origin, and how often a pulmonary lesion coexists or may later develop in that patient.

At the third instruction, special study is directed to variations of breathing in incipient and advanced cases, with emphasis on the former group. The students are shown cases having variations from the normal, chiefly slight prolongation and blowing of expiration, while other cases showing granular breathing or even slight suppression of breathing are exhibited.

I try to avoid the term bronchovesicular, but impress upon the students the necessity of recognizing slight changes in either inspiration or expiration, or both.

Alongside of these cases are shown patients demonstrating advanced lesions, in which blowing upon both inspiration and expiration, with a definite pause between the two, is present. I make no attempt to distinguish between bronchial, amphoric and cavernous breathing, but am content to point out qualities of breathing which indicate advanced pathological changes. Three cases of advanced tuberculosis, with only a slight amount of disease on one side, are selected for this demonstration, and the entire section auscultates each patient. Opportunity is also given to review briefly the instruction of the preceding periods.

Then the histories of all cases are given to the section, followed by the anatomic diagnoses. After this there follows a talk on the insidious onset of tuberculosis, with the modes of abrupt onset again reviewed.

The principal subject of study at the next session of the section is a consideration of inspection and palpation. One who sees any number of truly incipient cases of pulmonary tuberculosis knows that frequently all physical signs are negative, or that only a few fine crackling râles after cough are present, or possibly granular breathing is the only sign elicited. Therefore, generally speaking, inspection is not usually of value in the diagnosis of early lesions.

In cases of long standing, even though of slight extent, localized retraction, diminution of motion or lagging can be pointed out. There is no question that almost every moderately advanced case of pulmonary tuberculosis exhibits inspection changes which are very definite to any student. Nothing can be more easily demonstrated than the changes on inspection, which are revealed in cases of moderate pleural effusion.

Tactile fremitus, while the least valuable of all physical signs, is pointed out to the students in all three cases. The opportunity is given to review all the physical signs taught in previous instructions, after which the histories of the cases studied are reviewed, and especially the modes of onset are discussed. Following this, a brief and to-the-point talk is given on the symptoms of tuberculosis, and the diagnosis without physical signs is emphasized.

At the fifth session of the section the difficult subject of percussion of the lungs takes up the major portion of the hour and a half of study. It is generally recognized that percussion of the lungs is the most difficult of all physical signs of the chest to estimate properly. The students

are taught to pay special attention to the length of notes as well as resistance to the percussing finger. At the outset they are shown the comparison of percussion notes over base of lung, thigh and trachea. Having this as a foundation, the students begin with percussion of the bases anteriorly, noting the character of the findings and the similarity of the two sides. Assuming that the cases selected do not show basal changes, percussion is practised from side to side, and, approaching the apices, changes in length of note and resistance to the finger are pointed out. Then percussion from base to apex on each side is performed, and any changes found are thus compared with the normal. The slight unilateral changes are often detected in this manner. Each student then reviews voice changes, râles, breathing, inspection and palpation of their original cases, after which the abnormal percussion areas of the other two cases are pointed out. The students, as a group, are then given the histories and diagnoses of the cases studied, and this is followed by a brief talk on the pathology of tuberculosis.

For the sixth session of the section, three cases showing slight unilateral disease are selected, and I go through the examination step by step, recording on a chart the findings just as they are obtained. After noting spoken-voice changes in the case in the first room, the students check up this finding while I am making similar examinations in the other two rooms. Each feature of physical diagnosis of the lungs is similarly recorded and pointed out until the examination is completed. Near the end of this part of the instruction each subsection is given the history, laboratory findings and diagnosis of the case under study. Following the complete recording of physical findings by each subsection, the entire group is given a talk on the prevention and prophylaxis of tuberculosis.

At the seventh meeting of the section the students are divided into groups of three each, and cases of a similar type to those used in the preceding instruction are examined by the students without assistance from me. Each subsection is given the complete history and laboratory findings of their individual cases. The students must make out a chart, recording each phase of the examination at its completion, but not until after the entire physical findings have been tested. When the charts are completed I compare the findings of the students with my own data and point out any discrepancies. This takes up the entire time of the section.

At the eighth and final session the students make out their charts on a similar type of cases, the only assistance given being the histories and

laboratory findings of their individual cases. As each subsection finishes its examination, any discrepancies with my own findings are pointed out. At the completion of the chartings the entire section is given a brief talk on treatment, which emphasizes the importance of proper rest and feeding in pulmonary tuberculosis. It is my endeavor to point out to the students which types of cases can be successfully handled by general practitioners at home and which types should be referred to specialists or to sanatoria.

Throughout the course the students are taught the necessity of proper examination of the sputum, and they are urged not to neglect this procedure, irrespective of the diagnosis made. The importance of X-ray study is stressed, but the students are taught that it is secondary in importance to history and physical examination in the diagnosis of early or slight tuberculosis. The subjects of tuberculin and serological tests are briefly mentioned to acquaint the students with their place in diagnosis.

CONCLUSIONS

1. To teach the diagnosis of pulmonary tuberculosis to a group of 12 to 17 students in a very limited time the above method in my hands has proved superior to any other method.
2. The building up of a diagnosis enables the student to appreciate the importance of each step of the physical examination of the lungs.
3. The recording of each part of the examination as completed emphasizes the importance of careful, painstaking work.
4. The students have been almost unanimous in their interest and, in after years, have expressed the opinion that the course has been of great benefit.

Philip Challis Bartlett

1875-1924

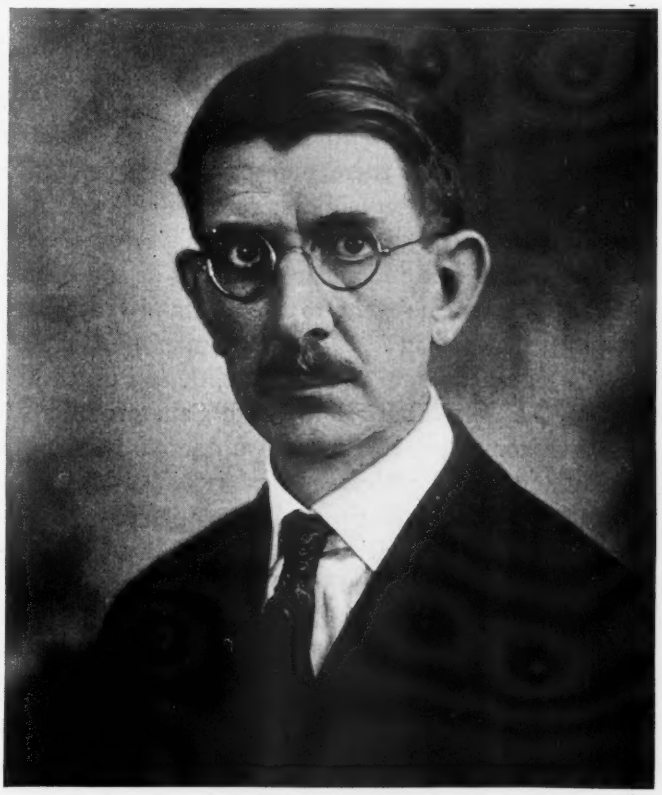
Bartlett of the Framingham Demonstration died suddenly, at forty-nine, on July 25, 1924, of an affection of the heart. This cardiac condition had been of long standing. He had been used to ill health during much of his life, and therefore, with characteristic pluck, played out the string to the end, though symptoms loomed more portentous and it became more and more plain to his friends that he was in a dangerous condition.

The Framingham Demonstration has taken its place as a model of medical research. At its very beginning it was seen that the first step in the study of community tuberculosis was to find out how much tuberculosis really existed there. It soon became apparent that this information, if it was to be accurate and complete, could come only from those to whom the sick, the disabled, and the run-down resorted for aid —from the whole body of practising physicians. It was plain also that this was not to be had for the asking or through edict: it would become available only when the Demonstration struck hands with the practitioners, and in a manner that convinced the latter that unselfish aid and instruction were available for them. The personality of the *liaison* officer thus became of decisive importance. The right man might do everything; the wrong one bade fair to wreck the Demonstration.

Bartlett was the man who, as the inquiry developed, came to carry the burden of this work. For several years he was the consultant of practically every physician in Framingham. The relation was not always an easy one; the work was frequently harassing; the most eloquent commentary on the man is that he was not long in winning the universal respect and affection of the entire Framingham profession and of the hundreds of patients who passed through his hands.

Bartlett's task was not showy work; it went on, always at home, in the background, and far from the gatherings that met everywhere to hear about the Demonstration and to acclaim it. But both Armstrong and Stone would certainly be the first to declare that no more earnest, honest and loyal work has ever been done. Both have always been

appreciative of what Bartlett meant to the Demonstration and of what he did for it. Armstrong speaks of "the tremendous contribution which Bartlett's work made, not only to the Demonstration, but to the very fundamental medical aspects of tuberculosis programmes everywhere." Stone declares that "Bartlett's special contribution to the programme will remain of permanent value."



Philip Challis Bartlett

All this was the work of character. Rather ill-favored physically, and of poor physique, Bartlett was an unusually attractive man. Earnest and kindly sincerity oozed from him and, as he got under way with his big, deep voice, you always felt safe and at home. He had a full, frank gaze, a rich sympathy and an innate regard for others that are not so common that, when met with, one does not notice them. You were sure that here was a man who would not intentionally touch a raw spot in you or hurt a single feeling. A certain modesty in bearing and put-

ting forward his views was one of his most noticeable characteristics; a first meeting was enough to dispel any suspicion that it may have been assumed, and one always felt that the man was bigger than he himself realized. He always wanted to know, to learn, and quite impressed one as being a man with a bent for inquiry and a passion for study that had not found full play.

There is not a soul in tuberculosis work who, having known Bartlett, can have felt anything save the most poignant regret at the news of his passing.

Philip Challis Bartlett was born in Newburyport, Massachusetts; educated in the public schools there, and graduated from Tufts College Medical School in 1900. He served later as house officer at the Boston City Hospital, assistant physician and pathologist at the Worcester Hospital for the Insane, and in similar capacities at the Danvers State Hospital. From Danvers he went to the Rutland State Sanatorium, as assistant physician, and in 1910 became Superintendent of this institution, after an absence from it for a year, during which he directed the building of the New Hampshire State Sanatorium at Glencliff. In 1913 ill health compelled him to give up active institutional work and he left Rutland. As he became more vigorous, he began private practice in Boston and used the medical out-patient department of the Massachusetts General Hospital for work and study. In 1916 he was appointed to the out-patient staff, and now became associated with Hawes and Miller, whom he helped to develop a large clinic of nonpulmonary tuberculosis. It was in 1917 that he went to the Framingham Health Demonstration, with which he remained until his death.

He died at his home at Newton Highlands and is survived by his wife, nee Miss Mary Fowler of Worcester, whom he married in 1905, one son, and his mother.

A. K. K.

EDITORIAL

CALMETTE'S PROTECTIVE INOCULATION AGAINST TUBERCULOSIS

From time to time the REVIEW has presented, in its Abstract Section, summary accounts of Professor Calmette's attempts to obtain a modified strain of tubercle bacilli, which while nontuberculogenic would be protective, and of the results of his immunizing experiments as these have developed (1). It will be remembered that, as the result of astonishingly prolonged and patient cultivation on bile-treated media Calmette and his co-workers had brought about profound and significant changes in bacilli originally of bovine type, that experiments on the immunization of cattle seemed unusually promising, that Calmette looked forward to trying protective inoculation of infants, and that plans were under way to test the immunizing capacities of his "biliated" bacilli on anthropoid apes at branches of the Pasteur Institute in French Guinea (at Dakar and Kindia).

A recent number of the *Bulletin de l'Académie de Médecine* (2) carries a communication from Professor Calmette (with seven associates), which brings these important studies up to date. It is doubtful whether any more significant work on preventive inoculation against tuberculosis has been done since the exceptionally searching investigations of Behring's *Bovovaccin* and Koch's *Tauramun* of two decades ago. At the same time the authority of the distinguished author lifts any recital of methods employed and results attained by him well above the attention ordinarily deserved by the usual run of studies in so difficult and treacherous a field. For these reasons we deem the following extended notice of Professor Calmette's latest contribution pertinent and, we hope, serviceable.

For more than twenty years, he says, he has without ceasing conducted experiments on the mechanism of tuberculous infection and reinfection and on artificial immunization against infection, and has at last succeeded in giving *young animals free from preëxisting tubercle* a true immunity against natural or artificial contact with tuberculosis.

He does this through protective inoculation with bovine bacilli that were altered in the following manner: During a period of thirteen years he made 230 successive cultivations of his germs on a medium of potato that had been cooked in ox-bile with a glycerol content of 5 per cent. After 230 subcultures the bacilli became thoroughly nonpathogenic for all animal species, including anthropoid apes. No matter how introduced into the body—intravenously, intraperitoneally, subcutaneously or by ingestion—they no longer evoked tubercle formation, though their "dosage" might be very large.

Thus deprived of all tuberculogenic power the bacilli were again returned to ordinary media, without bile, for cultivation. This was to make sure that their new properties were fixed and that their virulence had been permanently lost. Put back on the usual media they remained avirulent. Nevertheless, they retained their capacity to produce tuberculin, and, when inoculated into animals, rendered the latters' serum positive to complement fixation. In other words, while time and "training" on bile-treated media had robbed them of all power to call forth tubercle, it had not affected decisively their antigenic properties, that is, their ability to have the animal body respond with "immune-bodies."

That the tuberculogenic attributes of these bacilli were definitely lost, and could not be restored, became evident as repeated massive reinfections of already inoculated animals failed to set up tubercle. All tuberculizable animals, including man, tolerated perfectly even intravenous inoculations. The modified strain, with qualities thus definitely established, was accordingly designated bacillus *BCG*. Moreover, it had become so harmless that, when eliminated by the dejecta or milk from animals of experiment and scattered outside, it proved to be completely inoffensive for man and all other animals. Accordingly, it differed from all of the many other modified strains of tubercle bacilli, that had in the past been employed in artificial immunization, in one decisive particular. This was that while the materials of Richet and Hericourt, Behring, Koch, Theobald Smith, Webb and Williams, etc., conferred protection as they gave rise to tubercle formation in the animal under immunization, Calmette's *BCG* raised resistance yet without setting up anatomic change. Every student of tuberculosis will at once appreciate the enormous importance of this difference.

A great many tests of *BCG* on calves, rabbits, guinea pigs and monkeys without preëxisting tubercle have shown that "it confers upon these

animals a manifest resistance to artificial virulent infections that are surely fatal for control animals."

The *Annales de l'Institut Pasteur* for May, 1924 (pp. 371 et seq.) contains details of the experiments with *BCG* on cattle and small laboratory animals. Outstanding features of this part of the work have been as follows: Single inoculations of 50 to 100 mgm. of living bacilli (ground in a fresh, dry state) into the areolar tissue of the dewlap of young calves creates an immunity that will resist perfectly the intravenous inoculation of 5 mgm. of virulent bovine bacilli for as long as eighteen months. "*Although this latter dose is fatal for all controls, within six to eight weeks, from acute miliary tuberculosis, it never in any way disturbs the health of the vaccinated calves nor gives rise to a single tuberculous focus.*" (Italics Calmette's.) In rabbits and guinea pigs, given *BCG* subcutaneously, intravenously or orally, the effects of subsequent virulent reinoculation were analogous to those obtained in calves though they were more transitory. In general the immunity set up by *BCG* tends to fade in calves toward the end of the second year and in rabbits and guinea pigs at about the sixth month after preventive inoculation. These periods represent, quite likely, the duration of residence of the modified bacilli in the bodies of each species. That is to say, for almost two years *BCG* bacilli and the tissues of calves will maintain a relationship of *symbiosis*, while in the guinea pig and rabbit this lasts about six months. By the time that these respective periods have passed the bacilli of vaccination will "either have been destroyed by the normal processes of cellular digestion or they will have been eliminated via the emunctories natural for bacteria (bile, intestines, mammary glands)." Then the body becomes again nonimmune; and "virulent bacilli of reinfection, whether they be some that still exist intact or bacilli introduced anew into a body whose immunity has thus become extinct, regain or hold all their power as pathogenic bacilli,—power such as they would display toward a body free from anterior infection."

Unfortunately, *BCG* promises to be practical only in preventing virulent infection. It is effective "*only in subjects who are completely free from tuberculous infection.*" (Italics Calmette's.) In those already infected it acts just like inoculations of any other tubercle bacilli, attenuated or virulent, living or dead; that is, it is similar to the latter in that it increases hypersensitiveness to tuberculin and to reinfections.

Since in France and all other countries of our civilization 98 per cent of adult mankind and more than 40 per cent of mature cattle (5 years of age and older) react positively to tuberculin and thus disclose themselves as being already infected, "*vaccination against tuberculosis would appear to be applicable only to very young subjects, to the newly born and to young calves, in the first days of life.*" (Italics Calmette's.) Large doses of vaccine, after they had acquired anatomic tubercle, would arouse in them symptoms of intolerance.

I. Experiments on Animals: Calmette and his associates have carried on their prophylactic work among cattle in the Departments of *Seine-Inférieure* and *Seine-et-Oise*. Since 1921 they have vaccinated all young calves during the first five days after birth, and have then allowed the animals to grow up, exposed to natural contagion, without changing their place of residence or the ordinary living conditions of the herds to which they continued to belong. They have repeated vaccinations on the same calves yearly. What they have aimed to do is, within five years, to rid previously infected farms of tuberculosis, by gradually doing away with the nonvaccinated adult cattle and keeping only the vaccinated ones, as these, through the natural increase of birth, would replenish the herds. Up to May, 1924, they had vaccinated, in the manner described, 127 young calves, all of which remained in perfect health. Their stated conclusion is that at present they can "affirm that vaccination and annual revaccination . . . . . are absolutely *harmless*."

Their work with apes in French Guinea has been equally encouraging as far as it has gone. They are able to certify that the vaccination is harmless for apes and is also "indisputably efficacious." For instance, on December 24, 1923, their collaborator, Wilbert, put three monkeys in the same cage (the work is proceeding in Kindia in a noncontaminated environment). One monkey got 5 feedings, at 48-hour intervals, each of 5 cgm. of *BCG*, on December 24, 1923, and January 1, 1924. Another was given two ingestions of virulent human tuberculosis (*sic*) on January 9 and 11, 1924. The third was a control. On April 17 the control died with advanced tuberculosis of the abdominal viscera and lymph nodes. On May 2 the artificially infected monkey died with tuberculosis that was almost identical to that of the control. The vaccinated monkey has remained in good health. Other experiments have proved the harmlessness of *BCG* for chimpanzees and other types of anthropoids. Excessive doses, such as 25 cgm. of *BCG* by ingestion or 5 cgm. subcutaneously,

are without noticeable effect except a transient reaction of micropolyadenitis which appears about the eighth day and is gone completely after about a month. After smaller doses, 1 cgm. for example, there is not the slightest evidence of lymphatic tumefaction.

II. Attempts to Immunize Young Infants: The original plan, to inoculate with *BCG* the newborn infants of tuberculous mothers exclusively, was impossible of fulfilment. The subjects have been infants in the maternity service of the *Charité*. Some were inoculated during the summer of 1922; the others since the beginning of 1924. The results reported here refer to the former series.

During the first nine days of life (either on the third, fifth and seventh days or on the fifth, seventh and ninth days after birth) the infants were given three ingestions of 2 mgm. of *BCG* each, or a total of 6 mgm. The vaccine was always fed with a spoon, a half-hour before nursing, when the stomach was presumably empty. A total of 217 infants were thus treated. Of these, 39 have been lost sight of, while the other 178 have remained under observation. During the first eighteen months 9 of the 178 died. In only three of the 9 was the cause of death determined, and of these 3, two died of bronchopneumonia and the third of "gastro-intestinal troubles." All of the surviving 169 have developed regularly and without digestive disturbances due to the *BCG* or any other derangement of general health. The material has therefore been shown to be perfectly harmless for young infants.

Skin tests have been made on 53 of these infants, generally at about three months after the ingestion of the third dose. The test was negative in 88.7 per cent and positive in 11.3 per cent of the 53. Of the 6 infants who reacted positively, 3 were found to be in contact with bacillus-carriers. Five of the negative reactors had a tuberculous subject among their immediate ascendants and had been exposed to contagion.

"We do not pretend," says Calmette, "that the problem may be solved with our modified bacillus, nontuberculogenic yet still toxic and a producer of strong and active tuberculin. We only believe—and we have furnished the experimental demonstration of this—that its rational employment may perhaps be able to reduce notably the tuberculosis mortality and morbidity of young infants; of such, for instance, as the subjects of the black race brusquely transferred from the African tropics, where tuberculous infection is nonexistent, to our country of an old civilization throughout, which it has been widely diffused for centuries."

And he cherishes the hope that the practice of his method of immunization may be undertaken, on a large scale, on young infants living exposed to contagion; "for example, in families that include a member who is a 'sower of bacilli,' and in the maternity wards of hospitals."

No one, who is at all familiar with the literature of the past on preventive inoculation against tuberculosis, will rush in to render a final opinion on the efficacy and practicability of any new method until this method has had trial in many hands, in many lands, in many subjects. One thinks at once of the thousands and tens of thousands of cattle which had to be employed and closely followed for a decade and more before a proper balance could be struck on the value of preventive inoculations devised by men who are among our great names—Behring, Koch, Smith, Vallée. And there can be no doubt that until Calmette's methods have had similar scrutiny the merits of his *BCG* must remain *sub judice.*

Yet this is all the more reason why his material should be placed at the disposal of competent and accredited workers in tuberculosis, that it may be tried on a sufficiently large scale and backed by ample resources. In addition, Professor Calmette's achievements are so noteworthy and his reputation is so deservedly high, that, of themselves, they would almost seem to demand the most thorough testing of his methods. It is obvious that if *BCG* took thirteen years of cultivation, through 230 generations, to acquire, the repetition and extension of his experiments by other investigators must be done with material supplied by himself. Extraordinarily ample though the resources for scientific investigation may be in the United States, and blessed above all countries though she is in foundations and institutes for research, not one of the latter could be expected to repeat Calmette's work if this meant a decade and more spent in the preparation of material. Yet this work should be extended on a much larger plan and should be carried out by more or less independent and detached observers, and this, of all countries, with its favored economic and scientific outlook and its warm appreciation of the author's position in the tuberculosis world, is the place to have a large share in proving the value of Calmette's method. At this time, his reports of observations on infants can hardly be called more than suggestive, and it is questionable whether the time has arrived to observe the active immunization of children here. But the results in cattle have

progressed to a stage that leads one to hope fervently that there may be devised some plan whereby Calmette's *BCG* will be given the most thorough trial on these animals under auspices that are beyond cavil in the United States.

For one cannot help feeling certain that whatever will keep cattle from getting tuberculosis will also eventually be found to prevent the disease in man. From Jenner, through Pasteur, and down to our own day, the whole story of protective inoculation warrants this conviction.

A. K. K.

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CORRECTION

In the paper, *A Chemical Basis for the Treatment of Tuberculosis*, by Robinovitch and Stiles, August, 1924, REVIEW, vol. ix, pp. 587–612, the words "then the filtrate containing the thorium hydroxide was treated," in the first line, p. 591, should read "then the thorium hydroxide was treated."

CLINICAL STUDIES OF THE HEALING OF PULMONARY TUBERCULOSIS

I. THE ABSORPTION OF PULMONARY DEPOSITS[1]

J. BURNS AMBERSON, JR.[2]

During the past decade clinical observation, especially with the aid of the roentgen ray, has greatly clarified our conceptions of the healing of tuberculosis. The mechanism of this process, an understanding of which means so much in treatment and prognosis, is gradually unfolding itself, and new clues which offer engaging leads for the work of the future are presenting. Formerly it was generally believed that, once established in the lungs, tubercle never faded from the pathological picture except by fibrous or calcific encapsulation and replacement. Now there is proof that actual absorption of certain types of lesions does occur—a finding which illuminates many problems, and which, curiously enough, confirms the surmises of several students of past centuries.

Richard Morton (1), seventeenth-century phthisiologist and one of the first to recognize tubercle as a constant accompaniment of pulmonary consumption, made the original deduction, so far as I am able to ascertain, that such tubercle may disappear spontaneously. Witness the following quotation from his *Phthisiologia:*

> And without doubt the breeding of these swellings is so frequent and common that a Consumption of the Lungs would necessarily be the common Plague of Mankind, if those swellings did not vanish, or were not removed by Art as easily as they are bred at first: And indeed I have been used to think, not without reason, that as the more Benign Tubercles are wont to go off of their own accord, and that quickly, so more of them lay the Foundation of this great Disease, of which I am now treating, but only those which are in some degree Malignant, and ill-natur'd, and that are wont to putrefie sooner or later from some peculiar quality in their Nature, from what part soever of the Body they have their original.

[1] Read before the American Climatological and Clinical Association, at Atlantic City, May 1, 1924.

[2] Loomis Sanatorium, Loomis, New York.

This remarkable confusion of fact and fallacy—more true than not—is a testimonial of Morton's scientific reasoning.

Eighty-four years ago, C. J. B. Williams (2), another English clinician and a disciple of Laennec, wrote the following:

> I cannot bring morbid anatomy to prove the possibility of a cure in the earlier stages of phthisis; but I have the history of several cases in which the signs render it extremely probable that some of the depositions, which form the first stage of consumption of the lungs, had been removed by absorption.

To-day there is evidence, gathered chiefly by the study of serial roentgenograms, fully to substantiate the unerring prescience of this declaration. Likewise, the American, Samuel G. Morton, in his illustrations of Pulmonary Consumption, published in 1834, while less specific in his statement, recognized that "it is altogether probable that tubercles are sometimes absorbed."

In previous communications (3) I have described the orderly changes through which abnormal roentgenographic shadows pass as shrinking tubercle slowly vanishes from the pulmonary field. It was noted that usually at least a faint residuum, in the form of light studding or fine stippling of the trunks, remains indefinitely, although in a few instances even this may be lacking to mark the site of the former lesion. The barely visible remnants in most cases presumably represent tiny encapsulated tubercles which may remain permanently as such; or it is conceivable that they are in part the shadows of circumscribed hyperplastic lymphoid tissue. In either event they have not been found to cause clinical symptoms. Such absorption of pulmonary deposits is seen in many cases. Usually it occurs in limited areas, but not uncommonly it may be so striking and widespread as to cast doubt on the diagnosis of tuberculosis, were it not for the confirmatory support of other findings. This leads to a comment on the type of tuberculous lesion which is most likely to heal in this fashion.

With the exudative type, as conceived by Aschoff and his school, there may be more or less extensive cellular and serous infiltrations preceding caseation, which do not actually cause much destruction of the lung structure, which are to be distinguished from the productive types of tubercle and which may be absorbed, allowing restitution of normal anatomy and function. This much seems to be substantiated by competent observers, but beyond this there is a divergence of views. Aschoff (4), for instance, believes that caseation usually means destruction of

lung structure, which obviously can never be restored intact, and that caseous matter is not absorbed. Dunham (5), on the other hand, holds that he has demonstrated the absorption of caseous bronchopneumonia, and cites the experimental work of Gardner to support his contention.[3] I cannot presume to reconcile these views. It must be remembered, however, that the areas of caseation which disappeared from the lungs of Gardner's animals were minute. There seems to be no good reason why similar areas should not be absorbed from human lungs, but the case may be different with such degenerations large enough to be clinically demonstrable and to cause appreciable destruction of tissue. I am certain that the probability of resolution decreases more or less proportionately as the extent of caseation increases. In most cases in which caseation is clearly recognizable, as, for instance, in the immediate neighborhood of some cavities, complete absorption of the cheesy masses seldom if ever occurs. Perifocal or collateral inflammation may resolve, but the caseous nucleus of the lesion usually persists indefinitely. It seems very possible, from our studies at the Loomis Sanatorium, that small deposits of this type may become roentgenographically invisible. Just how small they must be is a difficult question to answer, because from the roentgenogram alone it is not possible to discern precisely where cellular pathological changes end and caseation begins. From my observations it appears that, when the residual tubercle measures more than several millimetres in diameter after the absorption of perifocal inflammation, healing proceeds more often by fibrosis and calcification; and the same is true even of many smaller deposits (fig. 1c). This view is supported by the elaborate and detailed studies of Gräff and Küpferle (6), who have been able to make many comparisons between pathological specimens and the corresponding roentgenograms. These investigators deny the possibility of a restitution of normal lung structure and function, once caseation has become established. In the light of present knowledge, therefore, it seems reasonable to say that the inflammatory or exudative type of tuberculous lesion may become completely removed by absorption, and that this mode of healing predominates where perifocal reaction is most intense. The relative possibility or frequency of absorption of caseous residues requires further research.

[3] Doctor Dunham has since explained to me that he does not consider experimental pulmonary tuberculosis, as produced by Gardner in animals, and caseous bronchopneumonia in the human subject as entirely comparable. The caseous bronchopneumonia set up in patients by bronchogenic dissemination may, he feels, be absorbed.

Healing by absorption may occur in infancy and childhood as well as in adult life, according to the observations of Harms (7). He has noted this in inflammatory infiltrations constituting the "primary complex" of Ranke, as well as in the secondary generalizing lesions of childhood.

Provided lesions are of the type described, they may be absorbed regardless of their pulmonary location. Lungs containing deposits only in the lower halves may clear up in the same manner as under the reverse condition. With the usual type of infiltration, absorption of the lowermost conglomerations is noted first, and healing proceeds from below upward, obviously because the fresher, smaller, and less degenerated tubercles are usually below, while the older, larger, and more caseous ones lie toward the apex.

The time element in healing by absorption varies. In cases proceeding favorably and without interruption a marked change may be noted in six months (fig. 4b). Residual studding and stippling, however, may persist indefinitely.

In some of the cases observed at the Loomis Sanatorium, in which absorption of pulmonary deposits was striking, single or multiple tuberculous complications were present, and in these there was also a coincidental improvement (case record 2). We are not inclined to feel that such healing is more frequent in complicated cases, although some suggest an unusually high immunity in such cases, and Marfan's law bears on this point.

In a previous statistical study I have noted that the absorption of perifocal exudate almost always connotes lessened toxemia. There are several particular clinical features to which attention may be directed here, the first of which is the change in the functional state of the lungs as determined by spirometric readings of the vital capacity. Statistics covering this point are being gathered by Doctor Andrew Peters of the Loomis Sanatorium. We have seen a number of cases with a well-marked increase in the previously impaired vital capacity progressing as the pulmonary infiltration diminished or disappeared, and we have come to the conclusion that this percentage of increase is demonstrably greater with healing by absorption than by any other mechanism (case record 2).

A study of physical signs in these cases has shown us a surprising behavior of râles. Other signs, such as adventitious breath and voice sounds, usually change toward the normal, as one would expect, with the disappearance of pulmonary condensations, but often the distribution of râles remains as it was originally. Sometimes râles decrease, to corre-

spond with the clearing of the roentgenograms, but sometimes they persist over extensive pulmonary areas from which absorption of infiltration has occurred, and in which the roentgenographic markings are within the accepted normal limits (case record 3). In one case I have observed this anomaly lasting for five years after healing was well established; in others there has been a very slow and gradual disappearance of râles proceeding over a period of two or three years after absorption. The râles in these cases appear to be definitely moist and intrapulmonary; they may be fine or moderately coarse, and, while usually elicited only by expiratory cough, they are sometimes heard during quiet breathing. At times the râles are associated with slightly diminished or muffled breathing. They are apparently of no immediate clinical significance, because many of the patients are well and working, and usually no sputum is produced unless there is a residual cavity. Constitutional improvement usually corresponds with the roentgenographic mutations, in paradoxical contrast with the behavior of the râles.

The explanation of these râles, which often are indistinguishable—unless they be a little finer and drier—from râles heard over an early and definite infiltration, is problematical. They may be due to a persisting nonspecific or catarrhal bronchiolitis or alveolitis, to a slight bronchiolectasis as suggestsd by Riviere (8), or to some mechanical barrier to the blood or lymph drainage of the finer anatomic structures. Another possibility is that residual tubercles, so microscopic as to be indiscernible by roentgenographic methods, may remain seeded through the areas originally harboring gross lesions. In some such cases a close scrutiny of well-detailed roentgenograms reveals a barely visible fine stippling which is not present in the picture of the normal lung; and there is conceivably a further retrogressive stage when tubercles become even smaller.

This study emphasizes again the great and reciprocal value of correlated observations in pulmonary tuberculosis. If the mind is fair and judgment sound, it does not matter greatly whether the clinician contemplates his patient's physical signs or roentgenogram first: the essential thing is that he consider them together.

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Case Record

(Cf. figs. 1a 1b, & 1c)

1: Mr. R. R. R., aet. 17, admitted October 22, 1919. The onset of the disease occurred eleven months previously when he had "grippe." After four days in bed he returned to work, but had occasional night sweats, and pain in the right chest. In August, 1919, he had blood-streaked sputum, and in September on one occasion coughed up a mouthful of blood. He continued working, but noticed some shortness of breath, and in early October had daily fever ranging from 101 to 101.8°. He had lost 2.8 kg. body weight previous to admission. On entering the sanatorium, the physical signs indicated severe infiltration in the upper two-thirds of the right lung, with consolidation in the lower part of this area, cavitation in the upper lobe, and pleural thickening over the upper lobe. Stereograms confirmed these findings, except that no definite cavitation could be visualized (fig. 1a). Sputum production averaged 22 gm. daily in October, but dropped to 8 gm. in November. Tubercle bacilli were demonstrated microscopically in the sputum in October, November, December and January. The patient did well from the beginning of treatment, and gained from an admission-weight of 51.72 kg. to a maximum of 65.74 kg. in March, 1921, when he was taking a moderate amount of exercise. The tubular quality of the breath sounds over the upper third of the right lung gradually lessened, and in April, 1920, had almost disappeared; after this the sounds became bronchovesicular. In June, 1920, the patient had acute appendicitis, necessitating operation; tonsillectomy was also performed. He recovered satisfactorily but lost weight. The pulmonary lesion continued to be retrogressive, and the stereogram of July 30, 1920 (fig. 1b) confirmed the physical findings of marked absorption of the infiltrated and consolidated area of the right lung. Tubercle bacilli were never demonstrated in the sputum after January, 1921, and sputum was usually absent after July, 1921. The patient continued to be underweight, apparently because of peritoneal adhesions interfering with digestion, but his general condition otherwise remained good, and he was able to do a half-hour's light work after March, 1921; a year later he was doing a full day's work. This he has continued without interruption, his duties becoming increasingly heavy. In September, 1923, there was moderate dulness and bronchovesicular breathing over the upper third of the right lung, and a few fine and medium "dryish" râles were audible above the second rib and fourth thoracic spine. Figure 1c, taken November 22, 1923, shows well-established calcification beginning in the residual caseous deposits in the right upper lobe. The calcification was first apparent in a picture made in April, 1923, but was not definitely recognizable in June, 1922. This patient was given no other treatment except the routine hygiene and rest.

FIG. 1a

Dense infiltration in the upper part of the right lung with partial consolidation of the upper lobe. Lesion of the exudative pneumonic type. (Cf. case 1.)

FIG. 1b

Marked absorption of the pneumonic deposits shown in figure 1a. Residual caseous deposits of moderate extent with only slight perifocal inflammation. Small band of interlobar thickening at the base of the right upper lobe.

FIG. 1c

Further absorption with recognizable calcification of the caseous residue

Case Record

(Cf. figs. 2a, 2b, 2c, 2d & 2e)

2: Mr. H. C., aet. 33, admitted June 16, 1920. Ten years previously he had had pleurisy and cough, without expectoration, and lost weight and tired easily, but felt well after a month's rest. In September, 1919, following a cold, he had a persistent cough. In February, 1920, he began to lose weight, expectorate, and tire easily. He had fever, occasional night sweats, and streaked sputum for several days. On admission to the sanatorium, physical examination showed an old, apparently inactive lesion in the right upper lobe, and moderate scattered infiltration in the left upper lobe and upper part of the left lower lobe. Stereograms (fig. 2a) revealed a heavy infiltration of the right upper lobe, with a few small deposits immediately below it, and a small cavity near the apex; extensive infiltration with some fibrosis in the left upper lobe and upper part of the lower lobe, and cavitation in the upper third. The sputum averaged 73 gm. daily and was positive for tubercle bacilli. The body weight was 46.55 kg. (standard for age and height, 59 kg.). Tuberculous laryngitis was diagnosed in September, 1920, and a superficial ulceration of the left arytenoid was noted in the following December. An old tuberculous ischiorectal abscess became active and had to be drained in March, 1922. There was also a tuberculous enteritis, apparently of some standing and accompanied by cicatricial thickening in the cecum and ascending colon, which caused symptoms of moderate severity during 1922. The constitutional condition was unstable for a year after admission, during which time the patient was in bed frequently with a low fever. This was due in part to the complications, as the pulmonary lesions showed a tendency to heal slowly (fig. 2b and c). Later the toxemia gradually decreased, and regular walking exercise was taken daily after July, 1922, without untoward reaction. The sputum decreased, and remained below 20 gm. daily after May, 1910. On monthly microscopic examination tubercle bacilli were constantly present until October, 1922; after this they were found occasionally in concentrated specimens; after December, 1922, they were demonstrated only once (May, 1923). The case was classified as "arrested" on discharge. All complicating lesions became quiescent; the ischiorectal abscess continued to discharge a little; and there was occasional hoarseness, but no intestinal symptoms. The body weight was 53.6 kg. Vital capacity readings were as follows: December 19, 1921, 3100 cc., 80 per cent calculated normal; August 21, 1922, 3300 cc., 85 per cent; February 23, 1923, 3750 cc., 96 per cent. Figures 2a, b, c, d and e demonstrate the remarkable absorption of the pulmonary deposits, with almost total obliteration of the small upper lobe cavities. In addition to the usual treatment, this patient received a prolonged course of artificial and natural heliotherapy. He was given also tuberculin (O. T.) subcutaneously from September, 1921, until February, 1922, and again during June and July, 1922; this was finally discontinued because of slight activity of the laryngeal lesion, the maximum dose of tuberculin (0.001 mgm.) having been received in February.

FIG. 2a

Heavy infiltration of the right upper lobe with light deposits below this; less intense infiltration of the left lung decreasing downward. Lesions are predominantly bronchopneumonic in distribution. Well-marked perifocal exudate, especially in the right upper lobe. Cavitation recognizable in the upper parts of both upper lobes in the stereograms, but not so apparent in this reproduction. (Cf. case 2.)

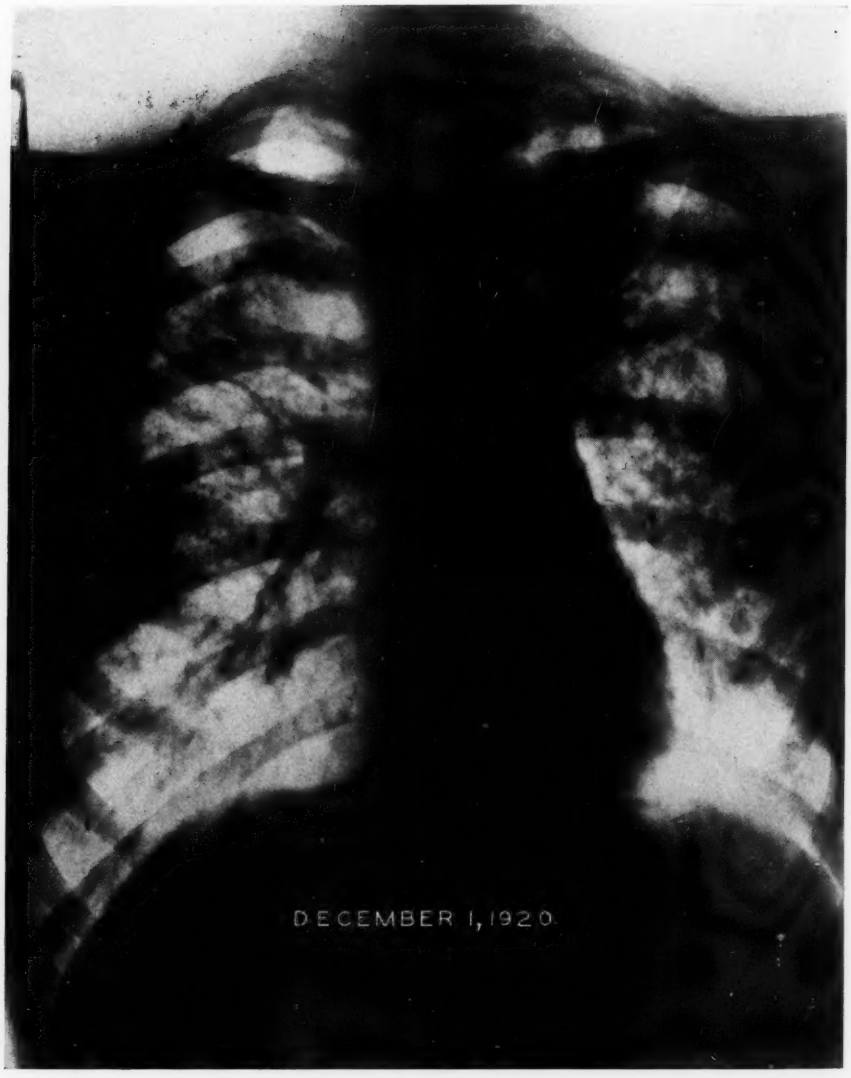

FIG. 2b

Striking absorption of the deposits on the right where the perifocal inflammation was most intense.

FIG. 2c

Further absorption of the lesion in both lungs, although the change has not been rapid. Note in case record that clinical progress was indifferent during this interval.

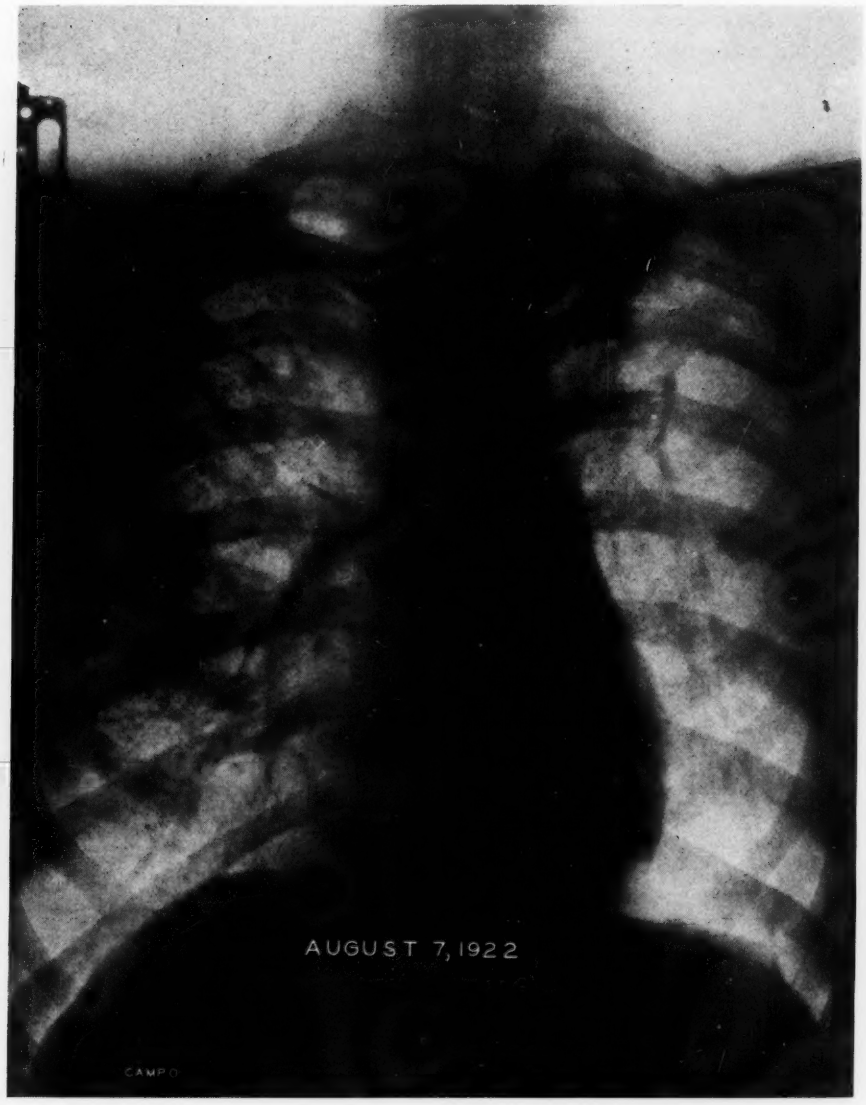

FIG. 2d

Striking absorption of the lesions from both lungs. Many formerly heavily involved areas now fall well within the "normal" roentgenographic limits of the adult lung.

FIG. 2e

To show that healing in this area was well established and maintained. Residual fibrous and fibrocaseous deposits in both upper lobes. Cavities almost entirely obliterated.

Case Record

(*Cf. figs. 3a & 3b*)

3: Mr. E. A. M., aet 21, admitted June 27, 1921. The patient never felt well after a mild attack of influenza in November, 1918. In September, 1920, he had hemoptyses repeated several times during one day, and after this he had fever for ten days, and two night sweats. After resting a month he returned to his work as a drug clerk, but in February, 1921, he began to lose weight and did not feel well. He also had an occasional rise of temperature. On admission he complained of tiredness and slight shortness of breath, but had no cough or expectoration; body weight, 53.9 kg. There was a heavy disseminated infiltration of the right lung, more marked in the upper and middle lobes, with slight cavitation in the upper third; also moderate infiltration extending from the hilum into the left lung below the second rib anteriorly (fig. 3a). For three months the patient had recurring exacerbations of symptoms, including chills, fever ranging up to 103° rectal, and intestinal manifestations indicative of tuberculous enteritis. Then the attacks became less severe and of shorter duration, and by the end of five months the condition had become so well stabilized that the patient was able to be ambulant. Thereafter his progress toward improvement continued slowly, being interrupted only on several occasions by a slight recrudescence of intestinal symptoms. In May, 1923, he started doing six hours' light work daily, and this he has continued since then. April, 1924, he weighed 76 kg., a total gain of 22.1 kg. The sputum has always been scant or absent, but a moderate number of tubercle bacilli have been demonstrated on two occasions. The marked absorption of pulmonary deposits is demonstrated by a comparison of figures 3a and b. This absorption was first appreciable in the stereograms of January 3, 1922, and from that time progressed steadily, until by September, 1922, the change was striking. Since then much of the fine stippling about the left hilum and in the lower part of the right lung has cleared away. There is a small residual cavity at the right apex which is being contracted by surrounding fibrosis. A notable feature in this case is the persistence of extensive intrapulmonary râles in regions where the stereograms appear normal or show only a little discrete studding of the trunks. The physical findings have not varied much in the last two years except that the râles are gradually clearing away on the left, and appear a little drier. On April 9, 1924, the following signs were noted: *Right:* Moderate dulness in the upper third, decreasing below this anteriorly. Breathing slightly diminished, and inspiration slightly harsh throughout anteriorly and above the angle of the scapula posteriorly. Bronchovesicular breathing with slightly consonating râles at the apex. Moderately coarse râles on quiet breathing throughout the upper third, extending to the base anteriorly and the seventh thoracic spine posteriorly, after cough, and decreasing in size downward. *Left:* Percussion note of fairly good quality. Expiration a trifle prolonged toward the apex. After cough a very few fine crepitations are heard in the interscapular region between the sixth and eighth spines. Vital capacity, 3700 cc. (76 per cent of calculated normal for surface area). In addition to the routine rest treatment the patient received artificial heliotherapy for the intestinal complication.

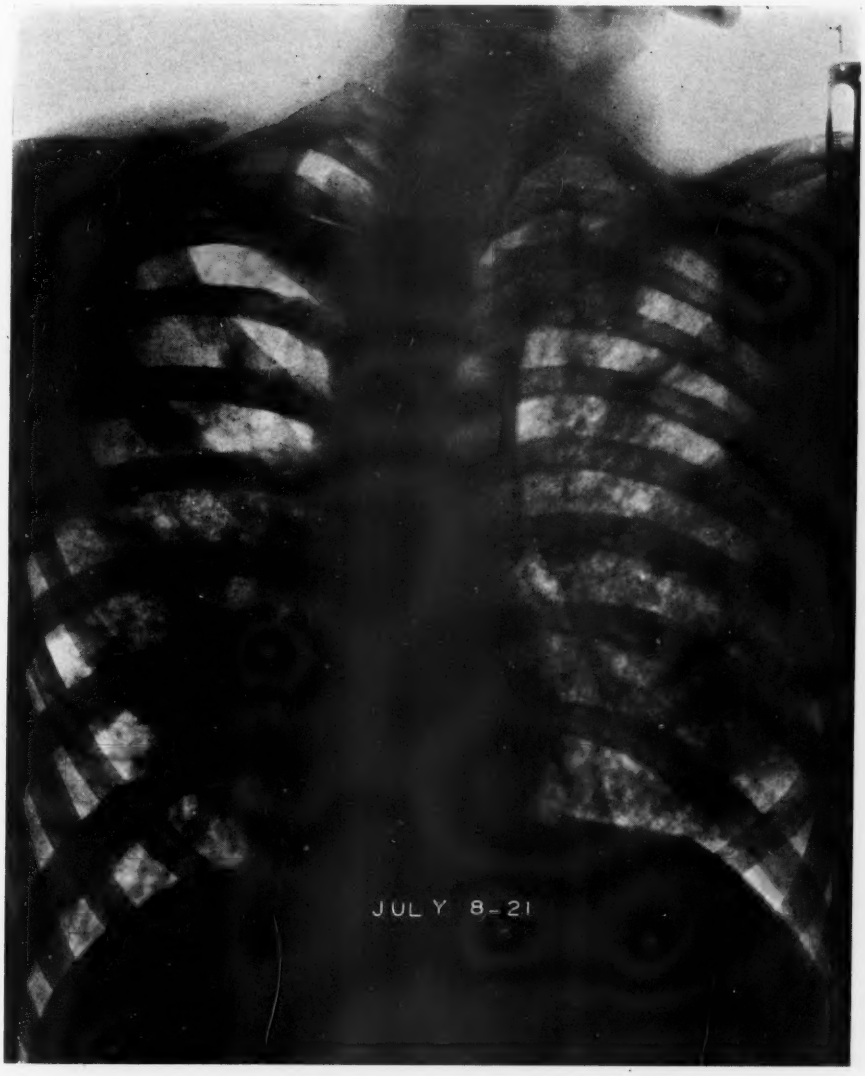

FIG. 3a

Heavy disseminated infiltration of the right lung, especially of the upper and middle lobes, with slight cavitation in the upper third; less intense infiltration extending from the hilum into parts of the left upper lobe. Lesions of the bronchopneumonic type with well marked perifocal exudation. (Cf. case 3.)

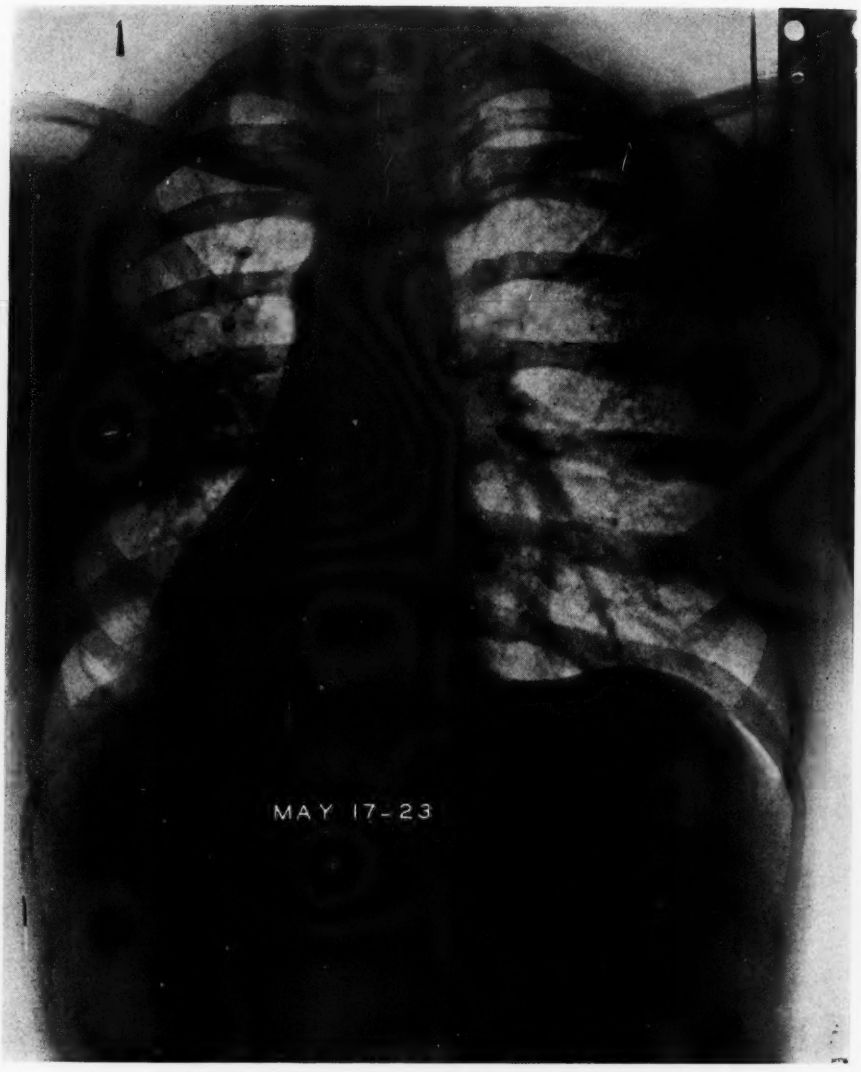

FIG. 3b

Marked clearing of the pulmonary fields, in many parts of which there is no apparent pathological change, although râles were still present. Residual fibrocaseous deposit and slight cavitation at the right apex.

Case Record

(*Cf. figs. 4a, 4b & 4c*)

4: Mr. R. J. B., aet. 22, admitted October 17, 1922. The onset of the disease was in July, 1922, when he had moderate hemoptyses, repeated during three days. He rested two weeks in bed and spent two more weeks in the country, where he gained 12 pounds in weight. He returned to work and continued at this, in spite of slight morning cough and expectoration, slight daily fever, occasional night sweats, and slight dyspnea on exertion, until he entered the sanatorium. On admission the physical and roentgenographic examinations showed fairly heavy infiltration of the right upper lobe with lighter infiltration disseminated below this; consolidation in the left lower lobe merging into lighter infiltration elsewhere; pleural thickening over the lower part of the left lung (fig. 4a). The patient had daily fever (up to 101° rectal), which persisted with decreasing intensity for two months after which the temperature became normal. He was kept in bed for another two months, after which graduated exercise was allowed and continued. In June, 1923, he started doing light clerical work at the sanatorium, and since January, 1924, he has been at his former occupation as a clerk in New York. His body weight was not subnormal while he was in the sanatorium, but he attained an excess above his normal standard of 67 kg. The sputum averaged 23 gm. daily on admission, but rapidly decreased after this. Tubercle bacilli were demonstrated each month until July, 1923, since which time there has been little or no sputum. The patient took no treatment except routine rest. The case is included to show the rapid absorption of pulmonary deposits of the exudative type, which sometimes occurs (fig. 4a, b & c). On November 20, 1923, examination demonstrated the persistence of fine and medium sized râles on the right, above the third rib anteriorly, and about the hilum between the fourth and seventh spines posteriorly; also similar râles below the fourth spine posteriorly on the left. Prolonged high-pitched expiration extending from the fourth spine to below the angle of the scapula, with intensification of vocal whisper, was also noted at this time.

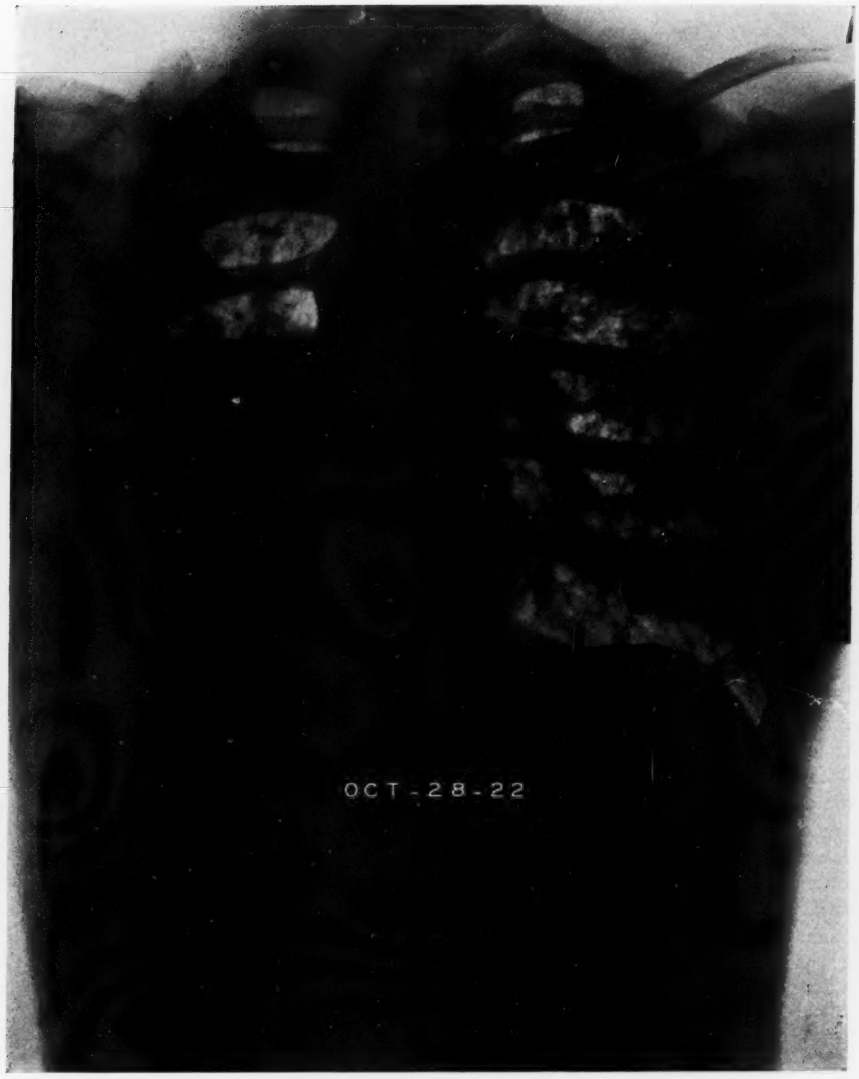

FIG. 4a

Moderately intense infiltration of the bronchopneumonic type in the right upper lobe with lighter deposits disseminated through the remainder of the lung; consolidation in the left lower lobe surrounded by light infiltration; moderate pleural thickening over the lower part of the left lung. Well marked perifocal exudation. (Cf. case 4.)

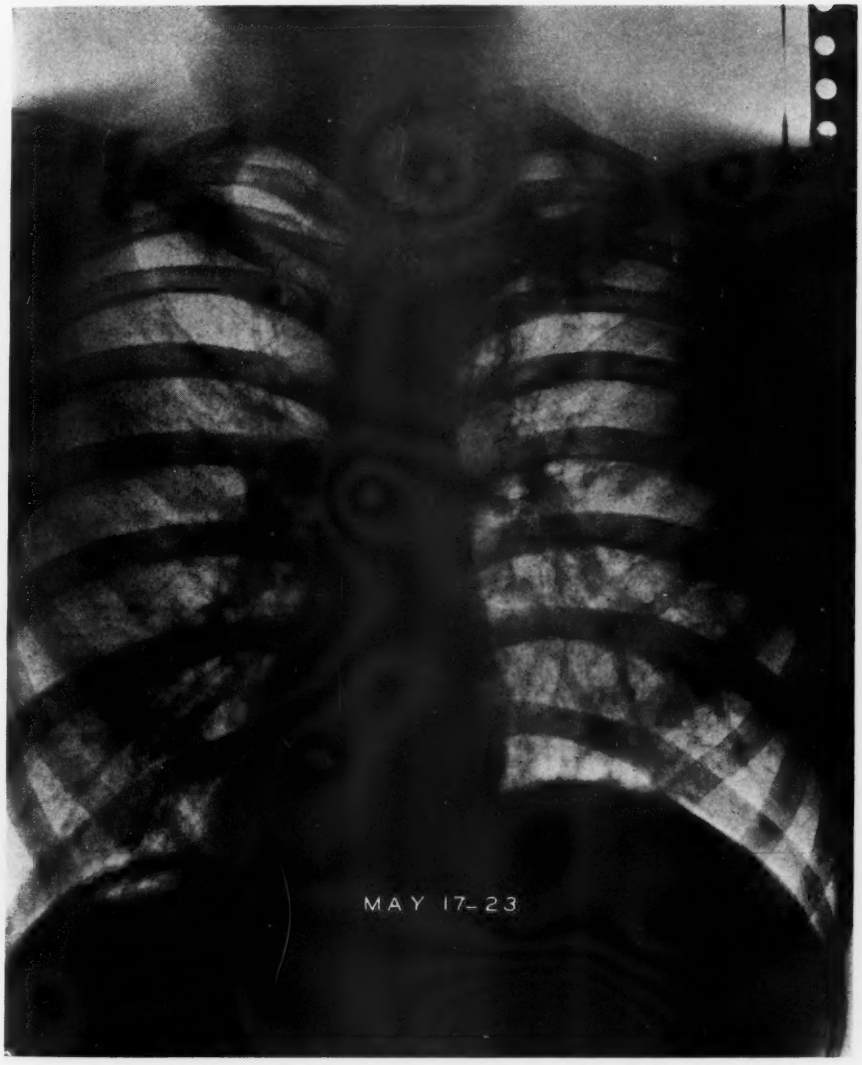

FIG. 4b

Strikingly rapid absorption of the lesions from both lungs. Perifocal exudate has been almost entirely removed.

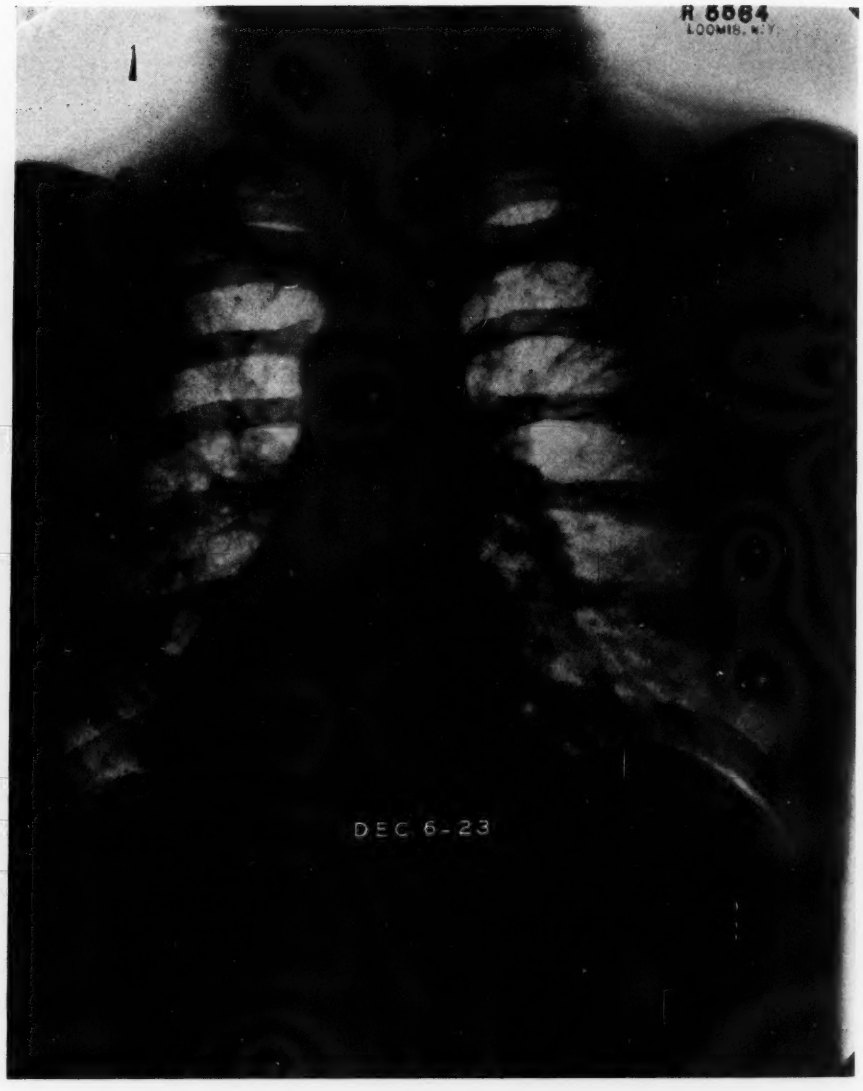

FIG. 4c

Further clearing of the pulmonary fields, many parts of which now appear normal. Residual partially caseous deposits adjacent to the left hilum where the original lesion was most intense. Pleural thickening on the left with diaphragmatic adhesions.

PATHOLOGICAL EVIDENCE OF FIRST INFECTION IN ASSOCIATION WITH ACTIVE PULMONARY TUBERCULOSIS[1]

EUGENE L. OPIE

In the present study previous attempts to correlate the pathological anatomy of tuberculosis with the well-known data obtained by experiments have been continued. It is evident that the tuberculosis of infancy resembles very closely the experimental tuberculosis of animals, whereas chronic pulmonary tuberculosis of adults has little resemblance to that produced by the usual methods of inoculation. The study has its origin in the conviction that the pathological anatomy and pathogenesis of tuberculosis in adults should be reëxamined in order to determine their relation to the focal infections of childhood.

The studies of Naegele (1) demonstrated for the first time the almost universal distribution of tuberculous infection which, unrecognized, proceeds toward recovery. Ghon (2) assembled evidence to show that tuberculous foci occur in children primarily in the substance of the lungs and only secondarily in the adjacent lymphatic nodes.

Several years ago I (3) showed that the healed or healing lesions present in the lungs of almost every individual after the age of 18 years have the characters of the tuberculosis of childhood and are in their essential characters distinguishable from the usual form of chronic pulmonary tuberculosis of adults which almost invariably has its origin in the apices of the lungs. Focal tuberculosis which in great part has its origin in childhood may be seated in any part of the lungs, usually below the pleura and not more frequently in the apex than elsewhere. It differs from apical tuberculosis (4) which begins in adult life or occasionally in the later period of childhood and pursues a chronic course characterized anatomically by abundant formation of fibrous tissue. It is especially significant that the focal lesion is associated with tuberculosis of the nearest lymph nodes, which is usually more conspicuous than

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the pulmonary lesion, whereas the apical lesion is unaccompanied by similar lymphatic lesions and in this respect resembles the tuberculosis of a previously infected animal which, as Koch showed, does not implicate the regional lymph nodes.

Tuberculosis of the apex in adults does not necessarily proceed to cavity formation and progressive tuberculosis, but indeed in most instances pursues a course which is not recognized by either patient or physician. This latent apical tuberculosis, omitting simple fibrous scars and including only those lesions which are characterized by caseation or by consequent calcification, occurs in one in five or six of white adults dying from causes other than tuberculosis. In the lungs which contain these apical lesions are found healed focal lesions implicating both parenchyma and adjacent lymph nodes, and there is little reason to doubt that the preëxisting focal lesion has modified the course of the apical infection. The character and position of the focal lesion furnish support to the view that the apical disease is not derived from the focal but represents a new infection, for in most instances the focal lesion is encapsulated and firmly calcified, and in fully one-half of these instances the two lesions are in the opposite lungs.

Latent, that is, unsuspected tuberculosis, may be intestinal in origin (5), and in one of every four among 67 young British adults quiescent or healed tuberculous lesions have been found in the mesenteric lymph nodes. When mesenteric tuberculosis has been present focal tuberculosis of the lungs has been scant or absent but apical tuberculosis may be found in association with the mesenteric lesion. In this country latent infection by way of the intestinal tract is uncommon.

In one instance of acute miliary tuberculosis (4) in an adult the disease apparently had its origin in a focal pulmonary lesion associated with extensive caseation of the nearest bronchial and peritracheal lymph nodes and, so far as it was possible to demonstrate by X-ray plates of the lungs made after death and by careful dissection, the individual had escaped tuberculous infection during childhood.

The study of obsolescent focal tuberculosis in relation to latent apical tuberculosis, to recognizable chronic pulmonary tuberculosis which may be conveniently designated phthisis, and to other forms of tuberculosis, has been continued with the aid of material collected in the Pathological Laboratory of Washington University. The present study has been limited to the lungs of white adults. I am especially indebted to Dr. W.

A. Hudson, Dr. H. S. Liggett, Dr. I. Y. Olch and Dr. N. S. L. Walsh for assistance in the collection and description of the lesions concerned. Roentgenograms of the excised lungs which have been essential to the study have been prepared with the kind coöperation of Dr. Sherwood Moore.

FOCAL TUBERCULOSIS OF THE LUNGS

Roentgen-ray plates made from the lungs after death furnish a satisfactory measure of the number, size and distribution of calcified foci within the lungs. Dissection of many lungs previously subjected to X-ray examination has shown that phleboliths, broncholiths and other forms of calcification, which are occasionally found, form an insignificant proportion of the calcified lesions of the lung. Calcified nodules clearly depicted in X-ray plates, and in most instances obviously situated both in lung parenchyma and in the adjacent lymphatic nodes, indicate the extent of healed pulmonary tuberculosis. In a former publication (6) I have described an arbitrary scale by which the extent of healed pulmonary tuberculosis might be roughly measured. This scale slightly modified is as follows:

Grade 1: One or several small nodules, usually one or two millimetres in diameter, are found in the parenchyma of the lung, and one or several small nodules are found at the hilum. The largest of these does not exceed 5 mm. in diameter. For the purpose of determining the relative extent of calcification it is desirable to adopt a well-defined limit separating grades 1 and 2, for these comprise approximately three-fourths of all lungs. Should the total area of calcification as indicated by the clearly defined shadows in the plate exceed 5 mm. square (25 square millimetres) the lung is placed in the next group.

Grade 2: There is a single nodule or several nodules within the lung substance from several millimetres to 1 cm. in diameter, and at the hilum of the lung larger masses which in unusual instances may be as much as 2 cm. across. This group makes up more than half of all lungs seen at autopsy in this country.

Grade 3: In a considerable number of instances it is evident that the individual has recovered from very advanced widely disseminated pulmonary tuberculosis of the type which has its origin in childhood. There are conspicuous scattered nodules in the lung substance and large calcified lesions at the hilum of one or both lungs, outside of the lung at the bifurcation of the trachea, or at the side of the trachea above the right bronchus. These calcified lesions may be 3 cm. across. With these extensive lesions, which occur in no inconsiderable proportion of all adults, there may be scattered encapsulated and calcified tubercles in the spleen, liver and occasionally in other organs. The lesion in the lungs and adjacent lymph nodes exceeds in extent many of those which cause general dissemination and fatal issue in childhood. It is evident that no sharp line can be drawn between latent tuberculous infection and tuberculous disease. In one instance (Autopsy 1907, plate 1, fig. 1) a calcified tuberculous mass the size of a pigeon's egg had perforated, by pressure, the wall of the oesophagus.

It is evident that the assignment of these calcified lesions to artificial groups does not furnish an accurate estimate of the severity of pre-existing tuberculous infection. Caseous lesions are not depicted in the X-ray plates but calcification serves as a rough measure of the extent of healing. The calcified lesions are very accurately depicted by the X-ray plates, and the separation into the groups described is readily made. The grouping affords a satisfactory basis for comparing focal pulmonary lesions in relation to age, race, etc. No noteworthy difference was found between men and women. In table 1 which includes only white adults the lesions are grouped by age.

TABLE 1

Calcified focal tuberculous lesions shown by X-ray plates of 115 lungs

	NO CALCIFIED LESIONS	VERY SMALL CALCIFIED LESIONS (GRADE 1)	CALCIFIED LESIONS (GRADE 2)	EXTENSIVE CALCIFIED LESIONS (GRADE 3)
18–29 years		6	15	2
30–39 years		2	13	1
40–49 years		5	11	1
50–59 years	2	8	14	5
60–69 years		4	14	
70 years		1	8	3
Total	2	26	75	12
Per cent	1.7	22.7	65.3	10.3

The table shows that the extent of calcification does not change materially with age until the later period of life. Calcification was absent or trivial in extent (group 1) in approximately one-fourth (24.4 per cent) of all of the lungs examined.

LATENT APICAL TUBERCULOSIS

The apical tuberculous lesions of adults exhibit characters which show wide variation in activity. The abundance of fibrous tissue is an index of the chronicity of the lesion. Apical tuberculous lesions may be listed in the order of their increasing activity as follows:

1. Latent apical tuberculosis found in those who have died with disease other than tuberculosis.

2. Chronic pulmonary tuberculosis or phthisis with an extensive apical lesion but no dissemination to other parts of the lungs.

3. Chronic pulmonary tuberculosis or phthisis with fibroid bronchopneumonia.

4. Chronic pulmonary tuberculosis or phthisis with tuberculous bronchopneumonia or, less frequently, with caseous pneumonia of lobar distribution (phthisis florida).

In a previous study (4) I have shown that apical tuberculosis which has produced no evident symptoms during life is found in the lungs of a considerable proportion of all individuals who have died from diseases other than tuberculosis. The lesion consists of fibrous tissue within which there are caseous or calcified areas. The lesion is usually from 2 to 5 cm. across and comes into contact with the indrawn puckered pleura at a point upon the outer, less frequently upon the inner, aspect of the apex, 2 or 3 cm. from the summit.

Among 74 lungs which were subjected to X-ray examination and carefully dissected after preservation in formalin, this lesion was found 16 times, that is, in more than one in every five individuals who had manifested during life no evidence of tuberculosis.

In the same lungs with the latent apical lesions, but with no evident relation to them, there has been in all instances focal calcified tuberculosis within the lungs and in the adjacent lymph nodes. In a former publication (4) there are diagrams which show the relative positions of the focal lesion of the lung, the lesion of the adjacent lymph node, and the latent apical lesion. In the present series the latent apical lesion has been unilateral in 13 instances, and among these the focal lesion has been on the same side 3 times, on opposite sides 6 times, and on both sides 4 times. The focal lesions of first infection were firmly calcified and very hard in 7 of the 16 instances with latent apical lesion; in 5 instances the nodules were calcified but mortar-like in consistence, so that they could be cut with a knife. In the four remaining instances there were both firmly calcified and encapsulated caseous foci of tuberculosis in lung and lymph nodes. These data indicate that the apical lesion is not derived from the focal lesion of childhood, for the latter are almost always completely healed and, in a large proportion of instances, situated in the opposite lung.

Roentgen-ray plates have been used to determine the extent of the calcified focal lesions found in association with the 16 instances of latent apical tuberculosis which have been cited. The lungs have been assigned to the groups previously defined and the result is as shown in table 2.

The table shows that the extent of these calcified foci of first infection accompanying apical lesions is almost the same as that of similar lesions in a larger series of individuals (115) who died with diseases other than tuberculosis.

CHRONIC PULMONARY TUBERCULOSIS (PHTHISIS)

If the course of chronic pulmonary tuberculosis of adult life is modified by the immunity conferred by a preceding infection it should be possible to find evidence of a first infection within the tuberculous lung. Orth (7) states that the lungs of those who have died with phthisis occasionally contain calcified foci indicating a preëxisting lesion, but in most

TABLE 2

Calcified focal tuberculous lesion in association with latent apical tuberculosis as shown by X-ray plates

	NO CALCIFIED LESIONS	VERY SMALL CALCIFIED LESIONS (GRADE 1)	CALCIFIED LESIONS (GRADE 2)	EXTENSIVE CALCIFIED LESIONS (GRADE 3)
18–29 years		1	1	
30–39 years			2	
40–49 years		2	1	
50–59 years			2	1
60–69 years		1	1	
70 years			2	2
Total	0	4	9	3
Per cent	0	25	56.3	16.2

instances, he says, lesions of this type are not found. With the aid of the roentgen-ray plate focal tuberculous lesions have been found in all instances of chronic pulmonary tuberculosis which have been examined (plate 1, fig. 2). These lesions have been classified in accordance with the grouping previously defined, in order to determine whether they differ in extent from those present in individuals with no progressive apical lesion. The result of this examination has been as shown in table 3.

In all save three instances the calcified focal tuberculous lesions depicted in the X-ray plate have been identified by dissection of the lung. When the plate is used as a guide the discovery of the calcified focus has been much facilitated, particularly when the nodules are small (grade 1). In the three instances cited (Autopsies 993, 2073,

and 2219) calcified foci were clearly defined by the X-ray plate in the peripheral part of the lung parenchyma and in the adjacent part of the hilum of the lung; these lungs were not preserved in formalin and consequently I had no opportunity to dissect them. In the remaining lungs the focal lesions were firmly calcified 9 times, mortar-like 3 times, in part densely hard and in part mortar-like 3 times. In one instance the lesion was thickly encapsulated and had a caseous centre, which contained enough calcium to cast a shadow on the X-ray plate.

It is noteworthy that the proportion of very small lesions (grade 1) with phthisis is much larger (42.1 per cent) than in a series of unselected lungs obtained from those who had not died as the result of tuberculosis

TABLE 3

Calcified focal tuberculous lesions in association with chronic pulmonary tuberculosis (phthisis) as shown by X-ray plates

	NO CALCIFIED LESIONS	VERY SMALL CALCIFIED LESIONS (GRADE 1)	CALCIFIED LESIONS (GRADE 2)	EXTENSIVE CALCIFIED LESIONS (GRADE 3)
18–29 years		3	1	
30–39 years		3	5	
40–49 years		1	1	
50–59 years		1	2	
60–69 years				2
70 years				
Total	0	8	9	2
Per cent	0	42.1	47.4	10.5

(no calcification, 1.7 per cent, and grade 1, 22.7 per cent, namely 24.4 per cent). No data are available concerning the relation between extent of first infection and resistance conferred upon the infected individual. With apical tuberculosis which has pursued a latent course the proportion of very small focal lesions (grade 1) is almost the same (25 per cent) as that of the unselected lungs and considerably less than that found with active pulmonary tuberculosis (42.1 per cent).

Table 3 shows that with phthisis very small calcified lesions (grade 1) were more frequent in early adult life, whereas extensive lesions (grade 3) were found only after 60 years. The small number of lungs permits no definite conclusion, but these relations suggest that small lesions confer scant resistance whereas extensive lesions confer a more lasting resistance which may disappear after a considerable period of years.

Varying degrees of resistance to the spread of pulmonary tuberculosis are suggested by the extent of tuberculous pneumonia produced by dissemination from the apical lesion.

In two instances there were densely fibrous apical lesions occupying the greater part of the upper lobe but unaccompanied by bronchopneumonia in other parts of the lungs. In one instance, Autopsy 1959, the disease occurred in a man aged 32 years, and the focal lesions present were small (grade 1); in the other instance, Autopsy 2070, the lesion occurred in a man of 55 years and were accompanied by larger focal lesions (grade 2).

In three instances tuberculous bronchopneumonia was present but had the chronic character indicated by an advancing margin of caseous tubercles surrounding a central area of pigmented fibrous tissue; the lesion is progressing at the periphery and healing at the centre. Fibroid tuberculous bronchopneumonia occurred in Autopsy 826, age 28 years, with focal tuberculosis of grade 1 and chronic renal tuberculosis; in Autopsy 1900, age 42 years, with focal tuberculosis of grade 2 (plate 3, figs. 5 and 6), and in Autopsy 2199, age 38, with focal tuberculosis of grade 2.

In the remaining fourteen instances of phthisis there was bronchogenic tuberculosis more or less widely disseminated throughout the lungs. In two instances there was caseous pneumonia occupying whole lobes; namely, in Autopsy 993, age 37 years, with focal tuberculosis of grade 1 and in Autopsy 2152, age 69, with extensive focal tuberculosis of grade 3 (plate 2, figs. 3 and 4). The variations in chronicity presented by these lesions bear no obvious relation to the extent of the latent first infection.

Factors other than specific immunity which has been conferred by a first infection doubtless modify resistance to the disease. In the group of cases just described there was a history of advanced alcoholism in two instances (Autopsies 823 and 834), diabetes mellitus in one instance (Autopsy 2167), carcinoma of the esophagus (Autopsy 1907), carcinoma of the colon (Autopsy 832), and syphilis (Autopsy 1900). Conditions which influence the nutrition of the individual doubtless alter resistance to the disease.

Experiments on animals furnish evidence that the resistance conferred by a first infection may be overcome by a second massive infection. The anatomic characters of chronic pulmonary tuberculosis of adults

furnish no evidence that it is derived from lesions acquired in childhood. The severity of the second infection may be in some part determined by the quantity of the infecting microörganism to which the individual is exposed. The influence of virulence of the tubercle bacillus upon the course of the disease has not been determined.

ACUTE MILIARY TUBERCULOSIS IN ADULTS

In a former publication (4) on the relation of apical tuberculosis of adults to the focal tuberculosis of children an instance of acute miliary tuberculosis in an adult colored man was described. There was a fresh caseous lesion near the apex of the left lung and extensive caseous tuberculosis in the lymph nodes at the hilum of the lung. Tuberculosis of the body of the fourth lumbar vertebra, psoas abscess and tuberculosis of the retroperitoneal lymph nodes had been followed by tuberculosis of the thoracic duct and acute miliary tuberculosis. Particularly noteworthy was the complete absence of preëxisting tuberculosis as demonstrated by a roentgenogram of the excised lung and by dissection. Pulmonary tuberculosis with the character of a first infection had occurred in a man 28 years of age and was followed by tuberculosis of the adjacent lymphatic nodes, localization in bone and general miliary tuberculosis. During the course of the present study a second instance of acute miliary tuberculosis in an adult colored man has been found, and in two white adults (Autopsies 1745 and 1968) the same lesion has occurred. It is significant that X-ray examination and subsequent dissection of the lungs have failed to demonstrate the presence of focal calcified lesions, for focal lesions are present in at least 98 per cent of all white adults and in approximately 92 per cent of colored adults. These four adults were affected with pulmonary tuberculosis which, acting like a first infection in early childhood, had caused progressive tuberculosis of regional lymphatic nodes and disseminated miliary tuberculosis. These observations indicate that acute miliary tuberculosis occurs in adults who are susceptible because they have escaped tuberculous infection during childhood.

In view of the foregoing observations it is questionable whether the penetration of a tuberculous lesion into the vascular system furnishes an adequate explanation of the occurrence of acute miliary tuberculosis. It is not improbable that tuberculous lesions in the previously uninfected individual penetrate very readily through the walls of blood vessels and

in consequence come into contact with the blood stream. Tubercle bacilli entering the blood cause acute miliary tuberculosis in the uninfected animal, but in the individual rendered resistant by preceding infection many bacilli are destroyed. Nevertheless, it would be rash to deny that miliary tuberculosis might occur in the presence of an old calcified lesion, for we are familiar with many factors which lower resistance to the disease.

CONCLUSIONS

1. Focal tuberculous lesions which have undergone calcification and are recognizable in roentgenograms of the excised lung are present in the lungs of 98 per cent of white adults who die from diseases other than tuberculosis. In one-fourth of these instances the lesions are of very small size (covering an area less than 25 square millimetres on the X-ray plate). In one of every 10 adults the healed lesions are as extensive as those which in children not infrequently cause fatal disseminated tuberculosis.

2. Latent apical tuberculosis has been found in the lungs of one in every five of the white adults examined. These apical lesions are invariably accompanied by evidence of a preëxisting focal infection which has had its origin in childhood. The character and extent of the focal lesions do not differ from those of similar lesions found in lungs of adults who have died from diseases other than tuberculosis.

3. Active pulmonary tuberculosis (phthisis) is always accompanied by evidence of a preceding tuberculous infection. Calcified foci of healed tuberculosis are present in the lung substance and in adjacent lymph nodes. These calcified lesions found in the lungs of those who die with phthisis are usually less extensive than those found in the lungs of adults who have died from other causes (covering in approximately half of the roentgenograms an area less than 25 square centimetres).

4. When acute miliary tuberculosis has occurred in adults it has not been accompanied by calcified lesions within the lungs, and the pulmonary lesion in these instances unlike the phthisis of adults has had the characters of a first infection. These observations indicate that general dissemination occurs because the adult has not been made resistant by infection acquired during childhood.

AUTOPSY RECORDS

Latent Apical Tuberculosis

Autopsy 580: A white woman, aged 54 years, died as the result of hysterectomy for carcinoma of the cervix. In the left lung there is fibrous tissue in an area approximately 2 cm. across, puckering the pleura upon the external aspect of the apex, and within it there are caseous spots. The lymph nodes at the hilum of the lobe show no noteworthy change. Three encapsulated calcified nodules occur in the right upper lobe, in lymph nodes at the hilum of the right lung and in lymph nodes at the bifurcation of the trachea. (X-ray plate, grade 2.)

Autopsy 678: A white man, aged 73 years, died from carcinoma of the colon. At the apex of the right lung there is a fibrous scar within which is found a caseous, partly calcified nodule of chalk-like consistence, 1.5 mm. in diameter. Within the substance of the left upper lobe there are 3 small encapsulated nodules with caseous, partly calcified centres. In lymph nodes at the hilum of the left upper lobe, below the left bronchus and at the bifurcation of the trachea, there are encapsulated nodules with soft, calcified, in one instance stony hard, centres. (X-ray plate, grade 2.)

Autopsy 756: A white man, aged 61 years, died with malignant hypernephroma of the kidney. A fibrous scar within which occurs a caseous area is found upon the median aspect of the left apex. Firmly calcified nodules occur in the lower part of the left upper lobe, in a lymph node nearby and in a lymph node above the right bronchus. Another lymph node in contact with the interlobular surface of the left upper lobe contains an encapsulated nodule, 2 mm. across, with caseous centre. (X-ray plate, grade 1.)

Autopsy 759: A man, 74 years of age, died from purulent peritonitis following resection of the cecum for carcinoma. At the right apex there is fibrous tissue occupying the entire summit and extending 1.5 cm. into the lung substance; within it is a calcified nodule 3 mm. across. At the left apex there is a similar fibrous scar with no calcification. Below the pleura, upon the median surface of the right middle lobe, there is a calcified nodule 1.2 cm. across, surrounded by 6 small nodules from 1 to 2 mm. in diameter, situated within the pleura. At the hilum of the lobe there are enlarged lymphatic nodes containing encapsulated caseous foci. Below the pleura, upon the posterior surface of the right lower lobe, there is an encapsulated nodule, 4 mm. in diameter, with calcified centre of mortar-like consistence. On the left side there are both calcified and encapsulated caseous nodules within the lung substance, and an encapsulated caseous focus is found in a lymph node at the hilum of the lung. The X-ray plate shows that some calcification has occurred in all of these lesions (grade 3). The spleen contains numerous spherical encapsulated nodules from 1.5 to 3 mm. in diameter, calcified in the centre. Similar nodules are found in the liver.

Autopsy 762: A man, aged 74 years, died from general arteriosclerosis and chronic nephritis. At the left apex, below the indrawn puckered pleura, there is a dry caseous spot, 1.5 cm. across, surrounded by a fibrous capsule. In contact with this caseous area there is a wedge of fibrous tissue with its base upon the pleura and its apex pointed toward the hilum; within it are caseous and calcified tubercles. Below the pleura of the right lower lobe there is a spherical calcified nodule, 4 mm. in diameter, and in lymph nodes within the lobe and at the bifurcation of the trachea there are larger calcified nodules. These are well seen in the X-ray plate (grade 2).

Autopsy 771: A man, 40 years of age, died with anthracosis of the lung and hypertrophy of the right ventricle. At the right apex there is a fibrous scar extending 2.5 cm. into the lung substance; it contains three caseous and partly calcified spots. Below the pleura of the left upper lobe there is a spherical mass, 1.2 cm. in diameter, with a fibrous capsule and a caseous partly calcified centre. The lymph nodes within the lung above the left bronchus and

at the bifurcation of the trachea contain caseous, partly calcified lesions. All of these nodules are seen in the X-ray plate (grade 2).

Autopsy 842: A man, aged 36 years, died from tabes dorsalis with pyonephrosis and septicemia. Occupying the outer and apical part of the right upper lobe are encapsulated caseous nodules, the largest of which is 2 cm. across. In the left lung, below the anterior surface of the lower lobe, is a firmly calcified nodule, 0.5 cm. in diameter. A lymph node at the inner margin of the left lobe near its hilum contains a hard calcified nodule 1.5 cm. across. (X-ray plate, grade 2.)

Autopsy 862: A woman, aged 73 years, died from general arteriosclerosis and chronic nephritis. (See AMERICAN REVIEW OF TUBERCULOSIS, 1920, iv, 637, and figure showing X-ray plate of lungs (grade 3).)

Autopsy 897: A man, aged 56 years, died with splenomyelogenous leukemia. At the right apex there is fibrous scar containing two small calcified nodules. Lymph nodes at the hilum of the left lung contain calcified nodules. The X-ray plate shows the presence of calcified nodules in the peripheral part and hilum of each lung (grade 2).

Autopsy 1004: A man, aged 57 years, died with chronic nephritis and syphilitic aortitis. At both apices there is fibrous tissue, within which are numerous calcified nodules. Throughout both lungs are spherical calcified nodules, from 1 to 3 mm. in diameter, and lymph nodes at the hilum of each lung have undergone great enlargement and massive calcification. Widespread calcification is evident in the X-ray plate (grade 3).

Autopsy 1027: A man, aged 38 years, died from multiple sclerosis. (See AMERICAN REVIEW OF TUBERCULOSIS, 1920, iv, 634.) (X-ray plate, grade 2.)

Autopsy 1875: A man, aged 41 years, died as the result of fracture of the 12th lumbar vertebra. At the left apex there is an indurated area surrounding a caseous nodule; it extends 1.8 cm. into the lung substance, and the overlying pleura is puckered. In the right upper lobe there is a hard calcified nodule, 4 mm. in diameter, and lymph nodes at the hilum of the lobe contain firmly calcified nodules. (X-ray plate, grade 2.)

Autopsy 1893: A man, aged 26 years, died from intracranial glioma. At the inner aspect of the left apex, 2 cm. from the summit and below the indrawn pleura, there is an encapsulated caseous focus, 1.3 by 0.8 cm. In the left upper lobe there is a round, caseous, partly calcified nodule, 0.5 cm. in diameter, and similar larger nodules occur in the lymph nodes at the hilum of the lobe. (X-ray plate, grade 2.)

Autopsy 1901: A man, aged 48 years, died with chronic aortic and mitral endocarditis. At the right apex there are scattered caseous nodules surrounded by fibrous tissue which is continuous with the pleura. Lymph nodes at the hilum of the right lung contain hard mortar-like calcified nodules of small size. A nodule seen in the X-ray plate (grade 2) at the right base was not found. At the left base is found an encapsulated caseous nodule 0.6 cm. across.

Autopsy 1964: A man, aged 68 years, died from epithelioma of the soft palate, tongue and cheek. At the right apex, occupying the summit and extending downward along the inner and posterior aspects for a distance of 7 cm., there are scattered fibrous scars within which are caseous nodules. In the lower part of the right upper lobe there is an encapsulated calcified nodule of mortar-like consistence. In lymph nodes at the right hilum there are similar calcified nodules. (X-ray plate, grade 2.)

Autopsy 1966: A man, aged 18 years, died with acute fibrinopurulent peritonitis following laparotomy. Occupying the inner half of the right apex there is an area of fibrous induration, 3 cm. across and extending into the lung substance a distance of 1.5 cm. It contains caseous nodules. In the left lung are hard but friable calcified nodules, and similar nodules occur in the lymph nodes at the hilum. (X-ray plate, grade 2.)

Phthisis with No Disseminated Tuberculous Bronchopneumonia

Autopsy 1959: A man, aged 32 years, died from general peritonitis, following appendicectomy occurring 6 years after onset of chronic pulmonary tuberculosis. Amyloid degeneration of the viscera has occurred. There is fibroid tuberculosis involving the right upper and middle lobes with cavity formation, and less extensive fibroid tuberculosis with cavity on the left side. There is no tuberculous bronchopneumonia in other lobes. Below the pleura of the right lower lobe are two small calcified nodules, and a similar caseous and calcified nodule is found near the hilum of the lung. The X-ray plate shows the presence of calcified particles within the fibrous tissue at the left apex, but the foci elsewhere are of small size. (Grade 1.)

Autopsy 2070: A man, aged 55 years, died with chronic pulmonary tuberculosis. Onset of symptoms was 5 years before death with cough during the last year and a half. There is fibroid tuberculosis, widespread through both upper lobes but more extensive and with large cavities on the left side. There is no tuberculous bronchopneumonia elsewhere. Small calcified nodules are found by dissection in lymph nodes at the hilum of the left upper lobe. In the X-ray plate are spots having the characters of calcified nodules within the lung substance, and the indurated tissue at the apices contains calcified particles (grade 2).

Phthisis with Fibroid Tuberculous Bronchopneumonia

Autopsy 826: A white man, aged 28 years, died with chronic pulmonary and genitourinary tuberculosis. The upper lobe is the site of fibroid tuberculosis, with cavity formation most extensive on the right side. Fibroid tuberculous bronchopneumonia occupies the uppermost part of both lower lobes and is evidently progressing from above downward. At the periphery of patches of bronchopneumonia caseation occurs, whereas within the centre there is pigmented fibrous tissue. The X-ray plate shows spots of apparent calcification in the peripheral part of the right upper lobe and in lymph nodes at the hilum (grade 1).

Autopsy 1900: A man, aged 42 years, died with chronic pulmonary tuberculosis, tuberculous laryngitis and meningitis, and tuberculosis of the intestinal tract. There was a history of syphilitic infection one year before death and the Wassermann reaction was positive. There is fibroid tuberculosis at both apices, more extensive and with small cavities on the right side. There is fibroid tuberculous bronchopneumonia, with patches formed by a fibrous centre and a peripheral zone of caseous tubercles. X-ray plate (plate 1, fig. 2) and dissection show a very hard calcified nodule in the right upper lobe, 6 mm. across, and in the adjacent lymph nodes there are firmly calcified masses of larger size. (Grade 2.)

Autopsy 2199: A man, aged 38 years, died with chronic pulmonary tuberculosis, tuberculous meningitis, chronic mitral endocarditis and chronic nephritis. Illness began with "influenza" six months before death. There is fibroid tuberculosis of the left upper lobe, with formation of a large cavity occupying a considerable part of the lobe (plate 3, fig. 6). In the left lower lobe there are large areas of fibroid bronchopneumonia, with caseous tubercles at the periphery and pigmented fibrous tissue in the centre. Below the pleura of the right lower lobe there are firmly calcified nodules, and at the hilum of the lung and bifurcation of the trachea there are lymph nodes containing large calcified masses. In the right lung there are small patches of acute tuberculous bronchopneumonia. Conspicuous calcified bodies are seen (plate 3, fig. 5), in the periphery of the right lower lobe and in the lymph nodes at the hilum (grade 2). Calcified particles occur in the fibroid tissue in the left upper lobe.

Phthisis with Tuberculous Bronchopneumonia

Autopsy 652: A man, aged 52 years, died with chronic pulmonary tuberculosis, and tuberculous pleurisy and peritonitis. There was atrophic cirrhosis of the liver and chronic mitral

endocarditis with insufficiency. The left lung is collapsed and its pleura is greatly thickened. There is an area of fibroid induration at the apex of the left upper lobe. Disseminated tuberculous bronchopneumonia occurs in both lungs. Small calcified nodules occur at the base of the left lung, in lymph nodes below the bifurcation of the trachea and above the left bronchus. (X-ray plate, grade 1.)

Autopsy 823: A man, aged 30 years, who had used alcohol in excess, died with chronic pulmonary tuberculosis and tuberculous ulcers of the colon. Almost the entire right lobe is the site of tubercle formation and dense fibrous induration. There is a large cavity at the right apex. Similar fibroid tuberculosis occurs throughout the greater part of the right lower and middle lobes. Patches of tuberculous bronchopneumonia occur at the base of the lung. The left upper lobe is in part replaced by fibroid tuberculous tissue in which are cavities. The uppermost part of the lower lobe contains numerous patches of tuberculous bronchopneumonia. The X-ray plate depicts a very small nodule in the lung substance, which is apparently calcified, and two much larger nodules nearer the hilum (grade 2). At the hilum of the left upper lobe within lymph nodes there are two hard calcified masses, 3 and 6 mm. across.

Autopsy 828: A man, aged 47 years, died with chronic pulmonary tuberculosis. The right apex contains a large cavity and was the site of fibroid tuberculosis. Smaller cavities occur at the left apex and there is disseminated tuberculous bronchopneumonia. The X-ray plate shows what appears to be a very small calcified nodule (1.5 mm. in diameter) in the substance of the left upper lobe and another of the same size at the hilum (grade 1). Dissection shows the presence of a calcified nodule in a lymph node at the hilum of the lobe.

Autopsy 832: A man, aged 28 years, died with carcinoma of the colon and chronic pulmonary tuberculosis. There was chronic apical tuberculosis with cavity formation on the left side, with disseminated tuberculous bronchopneumonia. The X-ray plate shows the presence of what appears to be very small calcified nodules (1 mm. diameter) in the right lung and at the bifurcation of the trachea (grade 1). Dissection shows the presence of two thickly encapsulated spherical nodules, 2 mm. in diameter, which occur below the interlobular surface of the right upper lobe and at the hilum of the lobe within lymph nodes. Encapsulated tubercles, of which the largest is 0.5 cm. across, occur in lymph nodes on the right side of the trachea just above the bifurcation.

Autopsy 834: A woman, aged 37 years, with a history of advanced alcoholism, died with chronic pulmonary tuberculosis and tuberculous pneumonia. At the left apex there is fibroid tuberculosis with advanced cavity formation. Extensive tuberculous bronchopneumonia occurs in both lungs. The presence of two round calcified nodules of 2 mm. diameter in the substance of the left lung and much larger calcified masses at the hilum is indicated by the X-ray plate (grade 2). In lymph nodes at the hilum of the left upper lobe above the bronchus are found on dissection several encapsulated nodules with caseous partly calcified centres.

Autopsy 901: A man, aged 53 years, died with chronic pulmonary tuberculosis with cavities at both apices, tuberculous bronchopneumonia and peritonitis and amyloid degeneration. The X-ray plate contains conspicuous nodules, indicating calcification (grade 2). In the substance of the left upper lobe is an encapsulated calcified nodule, 4 mm. across. Calcified masses, the largest 1.1 cm. across, occur in lymph nodes in the lung and near the bronchi.

Autopsy 1865: A man, aged 35 years, received an injury of the spine in a foot-ball game 17 years before his death. Three years after this injury there was pleural effusion and tubercle bacilli were found in the sputum. A nephrectomy was performed on the right side and a tuberculous kidney was removed. Resection of three ribs had been performed on the left side. The left lung which is collapsed is densely fibrous and there are cavities at the apex. There is a fibroid tuberculous lesion at the right apex and some tuberculous bronchopneumonia. X-ray plate and dissection show the presence of calcified nodules, the largest of which is 2.5 mm. in diameter, in the right lung and in the lymph nodes at its hilum (grade 2).

Autopsy 1907: A man, aged 60 years, died with carcinoma of the esophagus with dysphagia for 4 years. There is chronic pulmonary tuberculosis with cavity formation at the right apex (plate 1, fig. 1) and tuberculous bronchopneumonia elsewhere in the lungs. In the peripheral parts of both lungs there are in the X-ray plate (grade 3) several round nodules, apparently calcified and about 3 mm. in diameter. At the hilum of both lungs, within lymph nodes, are much larger calcified nodules. Below the bifurcation of the trachea there is a very large firmly calcified mass measuring 4 cm. across. It is in intimate contact with the esophagus and has caused perforation by pressure.

Autopsy 2073: A man, aged 30 years, died with chronic pulmonary tuberculosis and bronchopneumonia. There is a large cavity at the left apex. The X-ray plate shows a small nodule (1 mm. diameter), evidently calcified, in the substance of the right upper lobe and a somewhat larger nodule at the hilum (grade 1).

Autopsy 2149: A man, aged 30 years, died with chronic pulmonary tuberculosis and pyopneumothorax. His father, with whom he lived, died with tuberculosis 9 months before the patient's death. There is extensive fibroid tuberculosis throughout the left upper lobe with the formation of a large cavity. In the left lower lobe there is tuberculous bronchopneumonia with cavity formation. On the right side the great part of the upper lobe is consolidated; there is fibrous tissue at the apex, as well as caseation and cavity formation, and the process extends from above downward and into the upper part of the lower lobe. The X-ray plate shows a small nodule, 1.5 mm. in diameter, with the characters of calcification, in the substance of the right upper lobe and a group of similar nodules in the hilum nearby. A considerable number of calcified particles of irregular form occur in the midpart of left lung (grade 2). A calcified nodule, 1 mm. in diameter, is found by dissection in a lymph node at the bifurcation of the trachea.

Autopsy 2167: A woman, aged 23 years, who had suffered with diabetes mellitus for two and a half years, had had cough for six months. There is chronic pulmonary tuberculosis, with cavity formation at both apices, and tuberculous bronchopneumonia. In the left lower lobe there is a cacified nodule, 1.5 mm. in diameter, and near the hilum of the lobe a pigmented lymph node contains a calcified nodule 1 mm. across. Outside of the lung in contact with the left bronchus are two firmly calcified nodules, each about 3 mm. across. These nodules are well seen in the X-ray plate (grade 2).

Autopsy 2185: A man, aged 29 years, died with chronic pulmonary tuberculosis and tuberculous peritonitis. There was no history of cough or expectoration, but the patient had been short of breath for 6 months. Nephrectomy was performed on the right side. There is fibroid tuberculosis, more advanced in the right upper lobe, and widespread tuberculous bronchopneumonia. In the X-ray plate there is an ill-defined nodule in the periphery of the left upper lobe (1 mm. diameter), obscured by tuberculous bronchopneumonia, and a round well-defined nodule (0.5 cm. diameter) at the hilum nearby (grade 1). A few calcified particles are seen in fibroid tissue at the right apex.

Phthisis and Tuberculous Lobar Pneumonia

Autopsy 993: A man, aged 37 years, died with chronic pulmonary tuberculosis, tuberculous pneumonia involving almost the entire left lung and tuberculous bronchopneumonia of the right lung. At the left apex there is fibrous tissue in an area about 4 cm. across. The remainder of the lung is almost uniformly consolidated and caseous. At the right apex there is a fibrous scar, and in the upper part of the lower lobe there are patches of tuberculous bronchopneumonia. In the X-ray plate there is a clear spot, indicating the presence of a spherical calcified nodule in the substance of the left lower lobe, and a similar nodule at the hilum nearby (grade 1). Bronchial lymph nodes are enlarged but show no caseation.

Autopsy 2152: A man, aged 69 years, died with chronic pulmonary tuberculosis, tuberculous pneumonia, and thrombosis of the right femoral and iliac veins. He had had cough for one year. At the apex of the right upper lobe (plate 2, fig. 4) there is fibroid tuberculosis involving the inner and posterior aspects of the apex. There is no cavity formation. The left lower lobe is very voluminous and almost uniformly consolidated and caseous. A hard calcified nodule, 2.5 mm. in diameter, occurs in the substance of the left lower lobe, and a large calcified nodule is found in a lymph node at the hilum of the lobe. Lymph nodes at the bifurcation of the trachea contain calcified nodules. The X-ray plate (plate 3, fig. 3) shows the presence of numerous calcified nodules (grade 3).

Acute Miliary Tuberculosis in Adults

Autopsy 1745: A man, aged 19 years, died with acute miliary tuberculosis, tuberculous peritonitis and pleurisy, focal pulmonary tuberculosis, and tuberculosis of the peribronchial and mediastinal lymph nodes. In the substance of the left lung near the hilum of the lower lobe there is a lymph node 1.5 cm. across, containing small caseous spots. A second tuberculous lymph node of a smaller size occurs nearby. Outside of the lung below the left bronchus is a mass of black lymphoid tissue, 2.5 by 1.5 cm., studded with caseous areas. On an X-ray plate from the excised lungs there is almost uniform mottling caused by miliary tubercles. There are no calcified nodules in the lungs or lymph nodes. Miliary tubercles are present in great number in lungs, liver, spleen, kidneys, meninges, and choroid plexus.

Autopsy 1968: A woman, aged 19 years, died with acute miliary tuberculosis, and tuberculous peritonitis, salpingitis and endometritis. Below the pleura of the left upper lobe there is a round caseous nodule, 8 mm. in diameter, surrounded by a fibrous capsule. Nearby is a second similar caseous and encapsulated nodule, 4 mm. in diameter. Below, at the hilum of the lobe, there are three enlarged lymph nodes which contain caseous areas in part encapsulated, in part without encapsulation. Examination by means of an X-ray plate and by thin sections of the lung hardened in formalin failed to disclose any calcified nodules of focal tuberculosis.

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PLATE 1

FIG. 1. X-ray plate from lungs of Autopsy 1907, showing chronic pulmonary tuberculosis with cavity formation at right apex (the right and left lungs are reversed in the figure) and calcified nodules in left upper lobe and in lymph nodes at the hilum of the lung. There is massive calcification of lymph nodes at the bifurcation of the trachea; this mass has caused perforation of the esophagus.

FIG. 2. X-ray plate from lungs of Autopsy 1900 showing chronic pulmonary tuberculosis with cavity formation at the right apex (the right and left lungs are reversed in the figure). There is a calcified nodule in the peripheral part of the right upper lobe and larger calcified nodules at the hilum of the lung.

FIG. 1

FIG. 2

PLATE 2

FIG. 3. X-ray plate from lungs of Autopsy 2152 with fibroid tuberculosis at the right apex (the right and left lungs are reversed in the figure), caseous pneumonia of the left lower lobe and numerous calcified nodules in the lung substance and in peribronchial lymph nodes.

FIG. 4. Photograph of the lungs shown in figure 3 with fibroid tuberculosis of right apex and caseous nodules throughout the right upper lobe.

FIG. 3

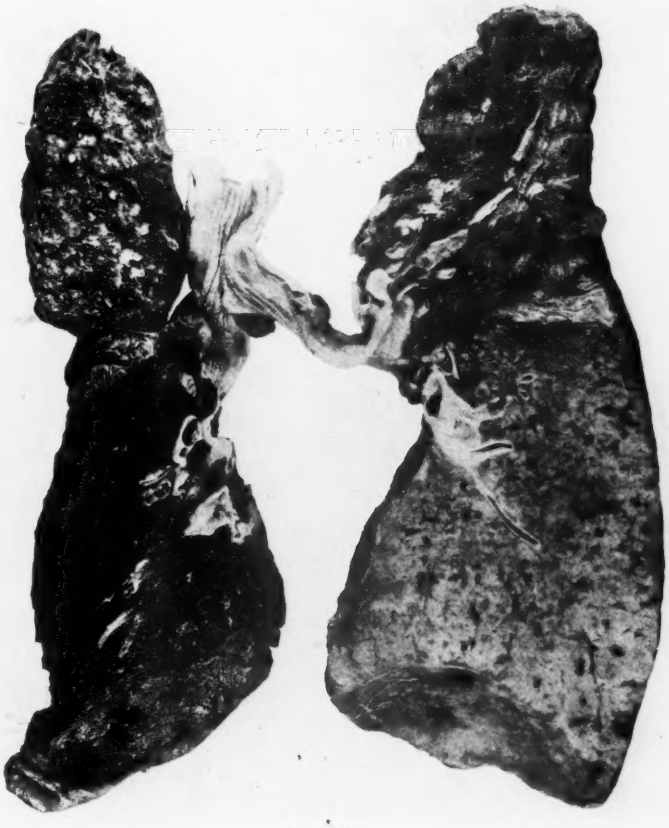

FIG. 4

PLATE 3

FIG. 5. X-ray plate of the lungs from Autopsy 2199 showing tuberculosis with cavity formation in the left upper lobe and calcified nodules in the peripheral part of the right lower lobe, in lymph nodes at the hilum of the lung and in lymph nodes at the bifurcation of the trachea.

FIG. 6. Photograph of the lungs shown in figure 5 with pulmonary tuberculosis with cavity formation in the left upper lobe (the right and left lungs are reversed in the figure), fibroid bronchopneumonia and calcified lymph nodes at the hilum of the right lung and at the bifurcation of the trachea.

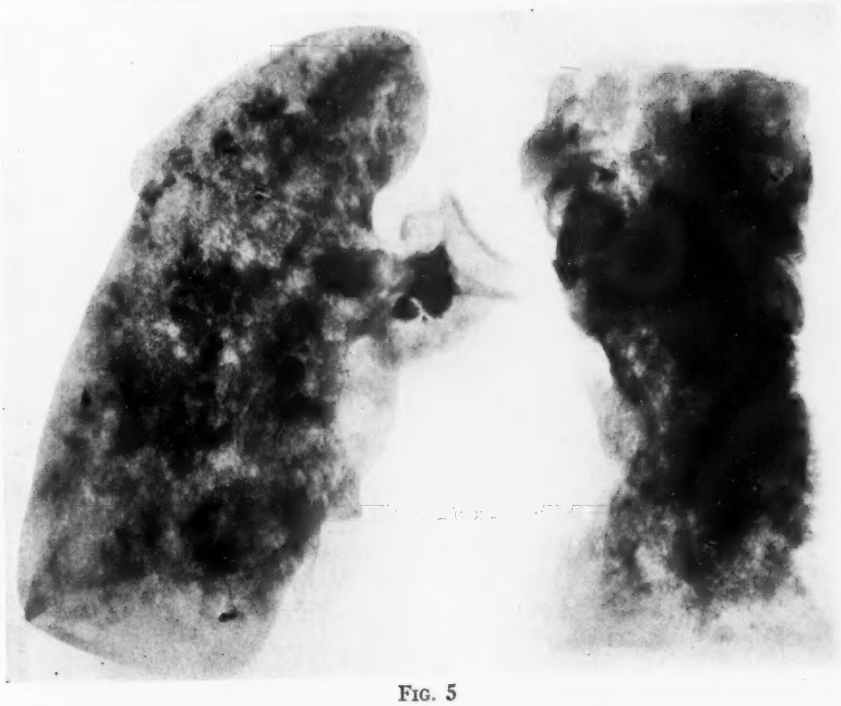

FIG. 5

FIG. 6

ACTIVE AND LATENT TUBERCULOSIS IN THE NEGRO RACE[1]

EUGENE L. OPIE

During the progress of a study undertaken to determine the relation of the focal tuberculous lesions which usually arise in childhood to the apical tuberculosis of adults it has become evident that the frequency of various types of tuberculosis differs considerably in the white and negro races. This study, made in St. Louis, furnishes evidence concerning the lesions found in that neighborhood and, though suggestive in reference to other parts of the country, it is not necessarily applicable to them. The number of autopsies on colored adults followed by X-ray examination of the excised lungs is small, and conclusions drawn from the study will perhaps require some revision. It is hoped that the tentative results may stimulate further study by those who can assemble larger numbers of observations.

LATENT FOCAL TUBERCULOSIS OF THE LUNGS IN ADULTS

The attempt was first made to determine the frequency of focal tuberculosis in the lungs of adults who had died with diseases other than tuberculosis. Table 1 gives the occurrence of calcified focal lesions as shown by X-ray plates in the lungs of 25 colored adults; the extent of the lesion is designated *grade 1*, *2*, or *3* in accordance with the artificial classification described in a preceding paper (1).

The percentages obtained with 115 lungs from white adults were as follows: no calcification 1.7 per cent; very small calcified lesions (grade 1), 22.7 per cent; calcified lesions (grade 2), 65.3 per cent; extensive calcified lesions, 10.3 per cent. The figures, though based on a small number of instances, indicate that healed, that is, calcified tuberculosis, is less extensive in the lungs of colored than of white individuals. The percentage of those with no calcified nodules was larger in the colored than in the white, and the percentage of those with no calcification or with very small lesions was considerably greater in the former, namely

[1] From the Henry Phipps Institute, University of Pennsylvania, and the Department of Pathology, Washington University, St. Louis.

40 per cent, than in the latter, in which it was 23.4 per cent. The focal tuberculous nodules of colored adults did not differ in character from those of the white.

LATENT APICAL TUBERCULOSIS

Latent apical tuberculosis has been found in the lungs of 16 of 74 white adults, that is, in approximately one of every five individuals or 21.6 per cent. It has been possible to study only 17 lungs of colored adults

TABLE 1

Calcified focal lesions shown by X-ray plates in 25 colored adults

	NO CALCIFIED LESIONS	VERY SMALL CALCIFIED LESIONS (GRADE 1)	CALCIFIED LESIONS (GRADE 2)	EXTENSIVE CALCIFIED LESIONS (GRADE 3)
18 to 29 years		1	1	
30 to 39 years		4	4	4
40 to 49 years	1		3	
50 to 59 years	1	3	1	
60 to 69 years			2	
70 years				
Total	2	8	11	4
Per cent	8	32	44	16

under the same conditions, and among these latent apical tuberculosis has been found only once, that is, in 5.8 per cent.

In this instance (Autopsy 1789) the man, aged 30, had had syphilis and a Wassermann reaction was strongly positive during his fatal illness. There was a large saccular aneurysm of the arch of the aorta; death occurred with pseudomembranous colitis and thrombosis of the pulmonary artery. The apices of both lungs contained fibrous scars. That on the left side was more conspicuous (plate I, fig 1), drew the puckered pleura inward and contained a calcified area of irregular shape 1 cm. across. At the base of the right lung there was a hard calcified nodule 1 cm. in diameter. At the hilum of the right lower lobe there were four large calcified masses varying from 0.7 to 1.5 cm. across. On the left side smaller calcified nodules occurred in the lower lobe and in the adjacent hilum. Below the bifurcation of the trachea there was a large calcified lymph node, 3.5 by 4.5 cm., and in immediate contact with the wall of the aneurysm to which it was firmly attached. In the wall of the aneurysm there was a defect, 0.6 cm. across, which opened into a cavity within the calcified lymph node. Within this cavity were particles of calcified material, some of which were from 1 to 4 mm. across and had facetted surfaces.

In this individual healed apical tuberculosis occurred in association with firmly calcified focal tuberculosis of the lung and massive calcified tuberculosis of adjacent lymph nodes.

ACTIVE APICAL TUBERCULOSIS

Among the white adults, of which autopsy records with roentgenograms made from the excised lungs were available, there were 19 instances of death from chronic pulmonary tuberculosis, and in all of these the lesion had its origin in the apices of the lungs. During the same period and under the same conditions there was among the colored only one instance of apical pulmonary tuberculosis.

The patient, a colored woman aged 20 years, came to the Barnes Hospital complaining of pain in the hip and inability to walk. She had had cough for six months. Pulmonary symptoms increased in severity and death ensued. The character of changes in the hip-joint was not determined. The anatomic diagnosis (Autopsy 1470) was: Apical tuberculosis with cavity formation; tuberculous bronchopneumonia; tuberculous pleurisy with adhesions; tuberculosis of peribronchial, peritracheal and mediastinal lymph nodes, with caseation; tuberculous ulcers of intestine with tuberculosis of mesenteric and retroperitoneal lymph nodes, with caseation; tuberculous peritonitis; disseminated tubercles of liver, spleen and kidneys. The upper lobe of the left lung was in large part consolidated and at the apex contained numerous small cavities. At the apex of the right lung there was consolidation. Throughout both lungs there was tuberculous bronchopneumonia. The peritracheal, peribronchial and mediastinal lymph nodes were caseous and much enlarged, some being 4 cm. across. (This description was obtained from the autopsy protocol and, as the tissue was not preserved, there was no opportunity for further examination of the lungs.) A roentgenogram of the lungs showed an ill-defined but opaque spot, 1.5 by 3 mm. and situated 3.5 cm. from the apex, and apparently within a wedge-shaped area of consolidation having its base at the summit of the apex; it suggested the presence of a focus with beginning calcification within an apical lesion. Three small ill-defined spots, the largest 1.5 mm. in diameter, had some resemblance to calcified spots at the hilum, perhaps within lymph nodes.

It is not possible to classify with certainty this instance of apical tuberculosis. The disease has pursued a much more acute course than that of phthisis in white adults, and at autopsy there is widespread caseation with little if any formation of fibrous tissue. In one respect this apical lesion differs from any of those found in white adults: there is extensive caseous tuberculosis of the lymph nodes at the hilum of the affected lung. Evidence concerning the occurrence of a preceding infection is uncertain, for ill-defined spots suggesting beginning calcification are found in the X-ray plate; but unfortunately the lung has not been preserved and search for these lesions has not been possible. This pulmonary tuberculosis which has occurred in a young adult has the character of an infantile lesion situated at the apex of the lung. An almost simultaneous infection of both apices may have caused a progressive lesion on the left side and a lesion with more tendency to heal on the right. Caseous tuberculosis of bronchial lymph nodes has not been

found in association with the phthisis of white adults, but with great depression of resistance, due perhaps to nonspecific factors such as malnutrition, it might perhaps occur.

TUBERCULOSIS OF LYMPH NODES

In two among the small number of instances of active tuberculosis in negro adults included in the present study there has been chronic progressive tuberculosis of lymphatic nodes. Among white people in this country lymphatic tuberculosis is much more frequent in children than in adults, and in the latter forms a very small proportion of all instances of tuberculosis.

A colored woman, aged 35 years, had noticed a lump in the abdomen the size of a goose egg four years before death. It increased in size, and she had been jaundiced. *Anatomic Diagnosis* (Autopsy 2172): Tuberculosis of substernal, peritracheal, peribronchial, anterior and posterior mediastinal, peripancreatic and retroperitoneal lymph nodes; tuberculous nodules in liver; amyloid degeneration of spleen, liver and suprarenals, and amyloid nephritis; chronic mitral endocarditis with stenosis; oedema of lungs. To the right of and anterior to the bifurcation of the trachea, there was a large nodular mass measuring 8 by 4 by 4 cm. There was a thick fibrous capsule surrounding firm, opaque, yellowish-white material. At the hilum of the right lung the peribronchial lymph nodes were much enlarged, in part fibrous and in part calcified. Similar nodes of smaller size were found at the hilum of the left lung. Tough and partly caseous tissue was in intimate contact with the trachea above its bifurcation. A roentgenogram of the excised lungs showed the presence of well-defined calcified spots of small size in both lungs, conspicuous calcified masses at the hilum of the left lung of which the largest was 2.5 by 1.2 cm., and smaller calcified bodies at the hilum of the right lung. The calcified spots at the hilum of the lungs appeared to be within larger masses which were doubtless the caseous lymph nodes described above. Peripancreatic lymph nodes formed a very large nodular mass extending along the entire lower border of the pancreas; they were firm and caseous. Retroperitoneal lymph nodes had a similar character. The liver contained conspicuous nodules, which had a tough yellowish-white centre and fibrous capsule. The largest were 3 cm. across, and the surface of the liver over them was puckered. Material from a peritracheal lymph node and from one of the hepatic nodules was inoculated into guinea pigs by Dr. H. H. Bell and found to contain tubercle bacilli of human type.

A colored man aged 30 years had had cervical adenitis for four years, when an operation was performed on the right side of his neck. The tonsils were also removed at this time, and he remained in a military hospital for three months. Swelling reappeared on the right side of the neck and later made its appearance on the left side. There was oedema of the legs and distention of the abdomen. *Anatomic Diagnosis* (Autopsy 2183): Tuberculosis of the cervical and gastric lymph nodes; tuberculous peritonitis; multiple ulcers of the stomach; ulcers of the ileum; amyloid degeneration of the spleen and amyloid nephritis. The lungs showed no noteworthy change. In an X-ray plate small spots indicating calcification are found in the peripheral part and hilum of each lung (grade 1). On the left side of the neck there were enlarged lymph nodes, three of which were 3 cm. in diameter; they were firm, but in the centre contained soft pus-like fluid. The bronchial, mediastinal and mesenteric lymph

nodes were not enlarged. Lymph nodes near the stomach were enlarged, several being 2 cm. across, and in their central part were soft and necrotic. On microscopic examination of the cervical and gastric lymph nodes the histological characters of tuberculosis were found.

In these cases there has been widespread progressive tuberculosis of lymphatic nodes which has pursued a chronic course. In one instance the disease appears to have had its origin in the lungs and peribronchial lymph nodes, but in the other instance the origin of the condition is obscure. In the first (Autopsy 2172) there have been calcified nodules within the lungs and adjacent lymph nodes (grade 2), and it is not improbable that these lesions represent a first infection from which chronic progressive tuberculosis of the lymph nodes had its origin. In the second instance calcified nodules within the lung are of small size (grade 1), and chronic tuberculosis of lymph nodes which persisted for two and a half years may have had its origin in the tonsils or in the gastrointestinal tract.

ACUTE MILIARY TUBERCULOSIS

In a former publication (1) evidence was assembled to show that acute miliary tuberculosis in adults is the result of a first infection. In instances of this condition healed focal lesions indicating a preceding infection have not been found and the pulmonary lesion, unlike the usual pulmonary tuberculosis of adults, has had the characters of a first infection.

Acute miliary tuberculosis has been found twice in colored adults. One of these cases has been described (2). There was a small caseous focus with no encapsulation near the apex of the left lung, extensive caseous tuberculosis of the nearest peribronchial lymph nodes, tuberculosis of the body of the second lumbar vertebra, psoas abscess, tuberculosis of the thoracic duct and acute miliary tuberculosis. Since no calcified lesions were found in the lung it may be assumed that the pulmonary lesion was a first infection, for it exhibited all the characters of those which occur in infancy.

In the following instance pulmonary tuberculosis of a type which occurs in young white children has been found in a colored adult and has been followed by acute miliary tuberculosis.

A colored woman, aged 26 years, was admitted to the Barnes Hospital in the seventh month of gestation with "cold in the chest" which had persisted during 6 weeks, shortness of breath and elevation of temperature. She had had two miscarriages and three full term

children, of whom two died within a few hours after birth. *Anatomical Diagnosis* (Autopsy 1915): Tuberculous focus at base of right lower lobe; tuberculosis of pulmonary lymph nodes at the hilum of the right lower lobe, of right bronchial and of tracheal lymph nodes; tuberculosis of right pleura; tuberculous peritonitis; tuberculous ulcers of ileum and colon; acute miliary tuberculosis. At the lowermost and anterior part of the right lower lobe, replacing lung tissue, occupying the pleura, and projecting upon the surface of the lung, there was a firm mass, in part gray and in part opaque yellow and caseous (text fig. 1); it was 6 cm. across and 2.5 cm. thick, smooth on its pleural aspect and nodular where in contact with the lung substance. In the midpart of the lower lobe was a spherical lymph node, 2 cm. in diameter, and almost wholly caseous. Below the right bronchus and extending to the bifur-

TEXT FIGURE 1. DIAGRAM SHOWING THE DISTRIBUTION OF PULMONARY LESIONS IN AUTOPSY 1915

There is a caseous tuberculous mass at the base of the right lower lobe and massive caseous tuberculosis of peribronchial lymph nodes within the lung, of lymph nodes at the bifurcation of the trachea and of lymph nodes above the right bronchus.

cation was an immense caseous mass of lymph nodes, measuring 4.2 by 3 cm., and above the right bronchus, beside the trachea, was a similar mass which was almost as large. The lungs and other organs were thickly studded with miliary tubercles. The mesenteric lymph nodes showed no evidence of tuberculosis. An X-ray plate (plate 1, fig. 2), made from the excised lungs, gave no evidence of calcification.

During the course of the study acute miliary tuberculosis has been found twice in colored adults, whereas among approximately four and a half times as many autopsies on white adults the same number of instances of disseminated miliary tuberculosis has been found. With the

small number of instances in view the relation vaguely suggests that the incidence of acute miliary tuberculosis is at least four and a half times as great in colored as in white adults.

DISCUSSION

The tuberculous lesions which have been found in white and colored adults may be classified as follows:

Tuberculosis in white and colored adults

	WHITE	COLORED
Calcified focal (as shown by X-ray plates)	113 (98%)	23 (92%)
Latent apical	16 (21%)	1 (6%)
Active apical	19	1
Lymph node	0	2
Acute miliary	2	2

A roughly approximate comparison between the two races may be made by multiplying the figures for the colored by four and a half, which represents the preponderance of whites in the autopsies which have been included.

The negro race in this country is not subject to the acutely fatal tuberculosis that has been seen among races which have been brought for the first time into contact with European civilization. They do not exhibit predominantly the acute tuberculous pneumonia, with caseation of the bronchial lymph nodes, described by Westenhoeffer (3) among the Indians of Chile. Nevertheless the foregoing study indicates that tuberculosis among them differs materially from that which affects their white neighbors. Chronic phthisis, with cavity formation and long continued expectoration of tubercle bacilli, is less common among the colored than among the whites, and more acute forms which afford relatively little opportunity for the escape of tubercle bacilli from the infected individual are common.

In Constantinople Deycke (4) did not find the prevalence of ulcerative phthisis beginning in the apices with which he had been familiar in other parts of Europe. This form of tuberculosis was not uncommon, but disseminated miliary tuberculosis, pulmonary tuberculosis without cavity formation, tuberculosis of lymph nodes and tuberculous peritonitis were predominant. Deycke pointed out that many parts of the Ottoman Empire of that day, for example, some regions of Anatolia and

of Arabia, were almost free from tuberculosis. He thought that the inhabitants of these regions were particularly susceptible to the disease when they came to the city and, when attacked by tuberculosis, suffered with a type of infection which tended to dissemination throughout the body.

In his book on *The Epidemiology of Tuberculosis* Bushnell (5) has attempted to explain the high mortality of tuberculosis among the American negroes. He thinks that they have been in contact with the white people so long that they are equally tuberculized. Their greater susceptibility to the disease is, he thinks, the result of malnutrition, overcrowding and other hygienic conditions.

The adjustment of virulence to the needs of parasitic existence has been discussed by Theobald Smith (6). The ability of the tubercle bacillus to invade the lung and produce a long-continued disease, during the course of which the microörganism is continually expelled from the host, is peculiarly favorable to the distribution and perpetuation of the microörganism. A more virulent microörganism, which quickly killed its host, would have little opportunity to find new hosts.

The human tubercle bacillus appears to have adjusted itself to the resistance acquired by the European races, which have been so long exposed to infection that almost every individual is infected in early youth. Certain Mediterranean peoples, such as the Egyptians and Greeks, have been exposed to tuberculosis for at least 30 centuries and probably longer. Where tuberculosis is prevalent it is the tuberculous adult who, by expulsion of infected and disintegrating lung tissue during a period of many years, is chiefly concerned in the dissemination of the disease.

Conditions are widely different when an uninfected people, such as the African negro, comes in contact with a race thoroughly saturated with tuberculosis. Members of the unprotected race acquire the disease when they come in contact with those who are suffering with phthisis. The acute forms of tuberculosis which result afford little opportunity for the dissemination of infection with the tubercle bacillus. In relatively isolated rural districts of the South contact with tuberculosis is doubtless less frequent than in the cities, the underlying conditions being similar to those which affect the propagation of measles. The colored adults, who acquire tuberculosis, in great part die with rapidly fatal pulmonary lesions, with acute miliary tuberculosis, or with other forms of visceral

tuberculosis, which afford little if any opportunity for the escape of the microörganism. The children of the race have in some instances scant opportunity for infection until they leave the rural districts. Confirmation of this suggestion by means of the tuberculin reaction is desirable. It is furthermore important to determine in what degree the migration of colored people to the cities of the north affects the incidence of tuberculosis among them.

The "tuberculization" of the race is a slow process retarded by the factors which have been cited. It is probably more advanced in some parts of the country than in others. The incidence of latent focal tuberculosis in the lungs of adults furnishes a rough measure of exposure to infection during childhood. In the neighborhood of St. Louis healing focal infection is less frequent in colored than in white adults, but this statement is not necessarily applicable elsewhere. The knowledge which is available indicates that the high mortality from tuberculosis in the negro race, the prevalence of acute types of the disease, the occurrence among adults of types which usually occur in white children, and the relative infrequency of chronic active and latent apical lesions in the negro are best explained by partial lack of immunization during childhood. Deficient immunization in early life is probably much more important than increased susceptibility referable to malnutrition and other conditions of living, or to natural racial susceptibility, but the operation of these factors cannot be excluded, and doubtless has some part in the high mortality of the colored race in this country.

CONCLUSIONS

The following conclusions are suggested by the foregoing study:

1. Focal pulmonary tuberculosis which has its origin in childhood is less prevalent (in the locality in which this study has been made) and less advanced in colored than in white adults; that is, a larger proportion of the colored escape tuberculous infection during childhood.

2. Chronic apical tuberculosis (phthisis) and latent apical tuberculosis are less frequent in the colored than in the white adult, and when pulmonary tuberculosis occurs in the adult negro it has more frequently than in the white the characters of a first infection.

3. Tuberculous lesions, such as acute miliary tuberculosis and tuberculosis of lymph nodes, which are often found in white children occur more frequently in colored than in white adults.

4. The American negroes are less thoroughly tuberculized than the white race.

5. The tuberculization of a race which has for the first time come into contact with tuberculosis proceeds slowly because the acute types of tuberculosis which make their appearance are not adapted to scatter the tubercle bacillus.

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Plate 1

Fig. 1. X-ray Plate of Lungs, Heart and Aneurysmal Sac of Autopsy 1789, Showing Latent Apical Tuberculosis with Calcification on Left Side (the Right and Left Lungs are Reversed in the Figure)

There is a calcified nodule in the right lower lobe, and calcified masses are found at the hilum of the right lung and at the bifurcation of the trachea. The mass at the bifurcation of the trachea has caused perforation of the aneurysmal wall. There are multiple calcified spots in the peripheral part of the left lower lobe and in lymph nodes at the left hilum.

Fig. 2. X-ray Plate from the Lungs of Autopsy 1915 Showing Acute Miliary Tuberculosis

Compare with text figure 1 which shows the distribution of pulmonary and lymphatic tuberculosis in the right lung. The X-ray plate shows the absence of calcified nodules within the lungs.

FIG. 1

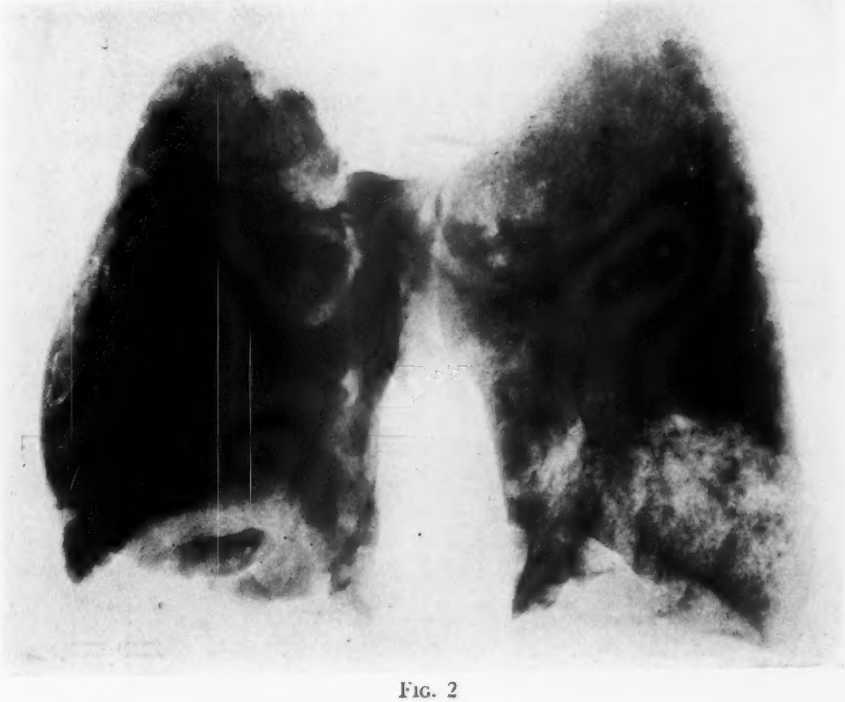

FIG. 2

RACIAL CHARACTERISTICS AS THE CAUSE OF THE HIGH TUBERCULOSIS DEATH RATE AMONG NEGROES[1]

CHARLES R. GRANDY

Norfolk, Virginia

In 1908 the writer published an article on the negro consumptive. At that time he believed that the large tuberculosis death-rate was due primarily to the fact that the negro had been living under the conditions imposed by civilization so much shorter a time than the white man that he had not been able to adjust himself, and that, in consequence, a mental rather than a physical predisposition was the basis of the disparity.

After sixteen years of observation in a clinic (averaging 27 calls a day last year) in which white and colored patients are seen on separate days, and records kept separately, I feel that it might be well to criticize this theory. In doing so I shall confine myself largely to statistics and experiences in my own city, where I come in contact with the negro in both the Departments of Health and of Education.

Let us look, first, at the comparative vital statistics in Norfolk. In 1907 the tuberculosis death-rate for whites was 135, and for negroes 433. In 1923 the Health Department gave the white rate as 48, and the colored as 214, though I believe that 60 and 240, respectively, would be nearer the truth. In other words, the death-rates in both races have been greatly reduced (the rate for the community having been cut in two), but the reduction in the white rate has been relatively greater. Still the reduction in the colored rate is much better than I dared anticipate when I read my first paper in 1908. But, when we compare what we are doing now against tuberculosis in both races with what we were doing in 1907 and 1908, the improvement can readily be accounted for. In the first place, Virginia now has an excellent sanatorium for negroes where good results are obtained. Secondly, a great deal has been accomplished here in the health education of the negro, as is being shown in

[1] Read before the clinical section at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 10, 1924.

his coming earlier for treatment and in his carrying it out better. And thirdly, his standard of living has improved. Still, there must be some fundamental reason for the tuberculosis death-rate for the negroes being four times that for the whites, even though a great improvement has taken place.

Let us first see whether there are any differences in nutrition and posture between the white and colored children which might have some influence on the problem, for according to Emerson, "The problem of tuberculosis is the problem of nutrition." It is our experience in the clinic, as well as the experience of the schools in Norfolk and Richmond, that the average colored child is considerably heavier for his height and age than the average white child.

In corroborating this I have tabulated the weight charts for 967 white school children and 822 colored children. These children are in the lower six grades, and their ages are from 6 to 12. I find that 24.6 per cent of the white children are 10 per cent or more underweight, as compared with only 14.6 per cent of the colored children. (In this work the older form of weight-charts as issued by the National Bureau of Education were used.) The two white schools investigated were in the better residential district, and had no children of very poor families. The two colored schools, while they were good average schools, naturally had, for the most part, children drawn from families who depended on day labor for their support, and the average family income was far below that in the white schools, which emphasizes our point that the colored child is naturally heavier than the white, even though the family income may be much lower.

It is furthermore our experience that we rarely find the fatigue posture in a colored child except in light mulattoes in whom the white characteristics predominate. Viewed from this standpoint it seems that we should have less tuberculosis in negroes than in whites, while we really have four times as many deaths among them. The probable explanation of this is that the heavier musculature of the negro makes him weigh more and stand better, and that, in consequence, the height-weight tables worked out for white children are not correct for colored children. Indeed, all we can get from this part of the problem is that the height-weight tables are not infallible and that external appearances are deceiving as indices of health.

As we have found more cases of open tuberculosis among colored than among white children, I have made a superficial investigation in regard to the possibility of bovine infection. In Norfolk the great majority of colored children are breast-fed, and when taken off the breast are given condensed milk, and seldom if ever get raw cow's milk. Indeed, the consumption of milk among colored families is relatively small. An opposite condition is found among the white people, yet the tuberculosis mortality is greater among colored children and young people than among the whites.

On the other hand there are differences in the course of the disease that have a bearing on the tuberculosis mortality in the negro. It is very apparent that tuberculosis often gets good headway in a colored case before there is much if any loss of flesh or energy, and we even oftener find a well-advanced case in which there is no history of cough. These colored people apparently feel pretty well, or at least do not give up and stop working, for they may come in with considerable fever and yet say they feel no inconvenience from it. It is difficult to decide in such cases whether the disease has been rapid, or merely slow and insidious, but in either case it means that the tuberculosis has advanced beyond the minimal stage before the patient has had warning of its presence, and thus has had his chance of recovery greatly reduced. Let us add to this the negro's habit of not noticing slight ailments, and we can readily understand why we do not diagnose tuberculosis in the negro earlier. All of this has a decided bearing on prognosis and death-rates among negroes.

As to effect of the negro's manner of living on his mortality rate, it is enough to say that it is certainly no worse than that of some of our foreign-born Jewish citizens, who apparently show the greatest racial resistance to tuberculosis. Is there really a lack of resistance in the colored race to this disease? I think there is a general feeling among medical men that there is, though there are still some who believe that the high death-rate is due to the fact that the negro does not get a fair show. It is interesting to note that Dr. H. G. Carter, who is getting splendid results at our State Sanatorium for negroes, has found the prognosis to be better in mulattoes than in pure negroes, the prognosis improving as the admixture of white blood increases.

We know that the negro differs from the white man in regard to his resistance to other diseases. Thus, all Southern medical men have

noticed that the negro can apparently overcome twice as much pyogenic infection as the white man. Syphilis also apparently runs a different course, it being next to impossible to elicit a history of secondary symptoms in a negro with tertiaries and a 4 plus Wassermann. And the tertiary manifestations also differ in the races, the negro's osseous and vascular systems being most markedly affected, while the nervous system seems largely to escape, such complications as tabes dorsalis and paresis being very rare.

Dr. Carter says that he has a far greater percentage of "the young adult type" of tuberculosis than occurs at a white sanatorium. This would indicate a high lack of resistance, but I doubt whether he is correct in thinking that it is due to the absence of contact, which is now encountered by the negro on every side. It appears to me rather to be due to a lack of inherited or racial resistance. This opinion is borne out by observation of cases that have returned from our white and colored sanatoria, which shows end-results to be much better in the whites, for of our cases that have returned from the sanatoria in the period, 1920–1922, 20 per cent of white cases have died, as against 38 per cent of the colored. It is also supported by the fact already reported that cases with very few symptoms show well marked lesions on physical examination, and that after they show symptoms the disease progresses rapidly. According to Krause, this lack of reaction may indicate a lessened resistance, for it is necessary to have an immunity in order to display certain symptoms. This "young adult type" is also found much more frequently in the young colored child than in the white; while the average age at which the disease develops is younger in colored than in white cases, which also is apparently due to the negro's lack of resistance, as these cases likewise have a worse prognosis than similar cases in white people.

I am sorry that I cannot give comparative statistics in regard to the relative frequency of miliary and pneumonic forms of tuberculosis in the two races, as my principal experience is in the dispensary rather than in the hospital. Still I feel sure, from my rather limited experience, that these forms are much more frequent in the colored race.

I do not, of course, deny that the negro's manner of living and his being not yet entirely accustomed to living the life the white man has gradually developed through the centuries, has an influence on his morbidity and mortality from tuberculosis. But when you see a big, strong negro with moderate infection go on and die in spite of treatment, and a

weak Jew with a great deal more trouble get well, the likelihood of a racial or inherited immunity stands out prominently over and above all other causes. I do not mean that tuberculosis among negroes cannot be reduced or that cases cannot be cured, for we have already proved the contrary, but I do mean that lack of racial resistance will make the problem a long, hard one, which will require the best efforts of our best men to solve.

SUMMARY

While our statistics show that colored children weigh more than white children, and are thus apparently better nourished, and have a better posture, there is more tuberculosis among these children and young adults than among the whites. Relatively, the same preventive and curative work is being done for the two races in Virginia, and the total tuberculosis death-rate has been cut in half in the last 15 years, but the improvement is greater in the white race whose rate is now about one-fourth that of the colored. The large tuberculosis death-rate in the negro is felt to be due to a racial lack of resistance, the result of his relatively short period of contact with the disease, rather than to bodily weakness or manner of living, though great improvement can be attained in this last respect.

THE INHERITANCE FACTOR IN TUBERCULOSIS

PREDISPOSITION OR IMMUNITY

GODIAS J. DROLET[1]

The theory that tuberculosis is inheritable dies hard. As the original protagonists of that idea have been driven, because of lack of evidence, from a belief in the actual transmission of the disease from mother to child, they have retreated into the position that, if the disease itself be not inherited, then at least a predisposition to it is transmitted.

Support of the statement that predisposition to tuberculosis is inherited is sometimes sought from figures of the amount of tuberculosis in certain families, the histories of which, in most cases, have been gathered from institutions where practically only tuberculosis was considered. A control series of histories similarly taken from among the nontuberculous general population is rarely given by these observers.

Even if "family histories" of tuberculous patients should reveal a greater amount of tuberculosis, why be surprised? If actual infection of some member of a family, let us say of a child, has taken place from a parent, or a relative or a neighbor, or from an infected milk and food supply, why should not other children living in the same house be in greater danger of being infected than in a home where this tuberculous environment does not exist? The wonder really is that there should not be a general infection of all concerned, under such conditions. Who for instance, would take a healthy child of nontuberculous parents and expose it to the conditions just mentioned and still feel that there would not be danger of infection to an equal extent for that child? Or again, in the case of tuberculosis in an adult member of a family, due perhaps to overwork or insufficiency of proper food, or to living in unsanitary quarters, why should there be astonishment were we to find more tuberculosis among the wives or husbands or other adult members of the same household, sharing the same dangers and privations and exposure? After all, the life of the various members of a particular family is certainly going on under more uniform conditions

[1] Statistician, Research Service, New York Tuberculosis Association.

than that of other people. Therefore, the conditions making for tuberculosis in one member of that household should be expected to produce more cases of tuberculosis in the other members than would be the case in families not living under such dangers.

In cattle, the Bang Danish method of separating the newborn calves from tuberculous herds has clearly proved that the danger from tuberculosis lies in the opportunities for infection after birth. Calves so separated have been freed from tuberculosis. This result very recently has again been duplicated in America by the United States Department of Agriculture at the Kodiak Experiment Station in Alaska, where tuberculous high-prize cattle were successfully utilized "for the production of healthy offspring" (1). The successful results of the country placement service of the *Oeuvre Grancher* in France with children from tuberculous families duplicate the experience with cattle.

When speaking of the prevalence of tuberculosis it is necessary, nowadays, to make a practical distinction between tuberculous infection and tuberculosis as a clinical disease, even if the border-line be indefinite. The difference between the two is marked enough to be acknowledged by all able to appreciate the commonplace events of life, even if the exceptional and rarer happenings are more interesting. Among adults, practically all of us are infected, but certainly only a minority of mankind has tuberculosis as a disease.

I had the opportunity for a number of years to study tuberculosis in New York City at the large municipal institution of Bellevue Hospital, where the service was one of the most active and where I made it a practice to abstract the histories of all the nontuberculous individuals examined as well as those of the cases of tuberculosis. As compared with similar studies in sanatoria, the results are far more satisfactory. In the nontuberculous part of the population examined in dispensaries an ideal control group is available. The histories of some 7,500 people, both tuberculous and nontuberculous, examined during five years, namely between 1912 and 1916, were first systematically abstracted to be studied and analyzed later—an opportunity which has offered itself only this year, so that obviously no support for a preconceived theory was being sought. Second, the cases, it will be noted, were drawn largely from the Bellevue District, a compact East-side section of New York City in which the majority of the dispensary clientèle live under similar conditions. Third, the histories covered in many instances

every member of the families under the observation of Bellevue Dispensary, as it is a common practice in the work of that institution, as in the work of all the clinics of New York City, to round up systematically and examine every member and contact of cases of tuberculosis. Fourth, the findings as to whether there was a history of tuberculosis in the parents of the patients were, at least in the case of all the children, based upon actual medical examination of both the parents and the children's group, and not upon hearsay or the indefinite statements of family members. Finally, the examinations were made by a large number of physicians, as this municipal institution is utilized by three medical schools, and there was, therefore, an unusual elimination of the personal equation in the findings.

TUBERCULIN REACTIONS

The spread of tuberculous infection in children as revealed by the tuberculin reaction was studied in 1,695 cases, of which 1,234 had a positive parental history of tuberculosis and 461 a negative history of tuberculosis in their parents. The greater amount of tuberculosis in parents of this group of children is, of course, due to the fact that at any tuberculosis clinic the children represent largely the offspring of tuberculous adults under the care of the clinic.

The results of the tuberculin reaction in the children of tuberculous parents, as compared with that in the children of nontuberculous parents, were practically alike. The details, qualified for the age of the children, are given in table 1. Among 373 children under five years of age, having a positive parental history of tuberculosis, 180, or 48 per cent, were found infected. Among 80 children of the same age from parents without tuberculosis, 38, or 47 per cent, were found infected.

Among 555 children between five and ten years of age, having a tuberculous parent, 382, or 69 per cent, were found infected. Among 183 children of the same age, with a negative parental history, 64 per cent were found infected.

Among 306 children, ten to fourteen years of age, of tuberculous parents, 75 per cent were infected. Among 198 children of the same age, with a negative parental history, 74 per cent were infected.

In the total number of children under fourteen years of age, namely 1,234, with a positive parental history of tuberculosis, 790, or 64 per cent, were found infected. In the total 461 children under fourteen

years of age from nontuberculous parents, 302, or 66 per cent, reacted to tuberculin. In other words, in New York City, in the children tested on the East-side, during the period of 1912 to 1916, no evidence was found of a greater amount of infection among those from homes where a parent had tuberculosis than among those free from parental tuberculosis.

TABLE 1

*Prevalence of tuberculous infection—tuberculin reaction (a)—in 1,234 children of tuberculous parents, and in 461 children of nontuberculous parents**

AGE	PARENTAL HISTORY POSITIVE (b)			PARENTAL HISTORY NEGATIVE		
	Tuberculin reaction			Tuberculin reaction		
	Positive	Negative	Per cent positive	Positive	Negative	Per cent positive
Under one	11	37	*24*	3	7	*30*
One	22	27	*45*	5	3	*63*
Two	43	39	*52*	4	6	*40*
Three	46	46	*50*	10	7	*59*
Four	58	44	*57*	16	19	*46*
Five	77	37	*68*	19	8	*70*
Six	82	35	*70*	21	17	*55*
Seven	79	43	*71*	29	17	*63*
Eight	75	32	*70*	32	10	*76*
Nine	69	26	*73*	17	13	*57*
Ten	68	19	*78*	35	17	*67*
Eleven and twelve	96	37	*72*	63	16	*80*
Thirteen and fourteen	64	22	*74*	48	19	*72*
Under five	180	193	*48*	38	42	*47*
Five to nine	382	173	*69*	118	65	*64*
Ten to fourteen	228	78	*75*	146	52	*74*
Total	790	444	*64*	302	159	*66*

(a) Cutaneous application.

(b) History of tuberculosis in either father or mother, and occasionally in grandparents.

* Compiled from the records of the Children's Division, Tuberculosis Clinic, Bellevue Hospital, New York City, 1912 to 1916.

Even if we should have found a higher percentage of tuberculin reactions in the children of tuberculous parents, it is open to doubt as to the proper meaning of this manifestation of the allergic state, at least as far as concluding that it would have been an ominous sign. Armstrong (2), you will recall, found at Framingham that the percentage of positive tuberculin reactions among Italian children was 51, whereas among the Irish children it was 30. Being aware that in this

country, in general, there is less tuberculous disease among the Italians than among the Irish, Armstrong significantly added: "Possibly it may be that *the tuberculin reaction measures the resistance of the child to infection.*" This is an interesting point to note, as some have been of the opinion that, at least as far as capacity for receiving tuberculous infection is concerned, no difference is known to exist in human stocks. I believe that, in a measure, the tuberculin reaction may even be a sign of actual and varying resistance to tuberculosis. How else explain the absence or disappearance of the reaction in the far-advanced cases, in children recently attacked by measles, in the later stages of pregnancy, or at certain seasons of the year as Hamburger noted? In any case, I have been unable to discover evidence from tuberculin testing at the children's clinic of Bellevue Tuberculosis Dispensary of a greater amount of tuberculous infection in the children of the tuberculous. As to the amount of tuberculous disease itself, in the children of tuberculous parentage, we will give further thought later, but for the moment we will draw attention to another authority for the lack of evidence of any greater amount of it in so called tuberculous stock.

Reiche (3) in studying the factor of heredity in cases of pulmonary tuberculosis in Germany, in several thousand cases investigated between 1895 and 1910, concluded that "there is no congenital or hereditary lack of resistance in the offspring of the tuberculous—no constitutional predisposition."

EXPOSURE TO TUBERCULOSIS

After investigating the prevalence of tuberculosis in children according to the tuberculin reaction, I studied at Bellevue the frequency of the known exposures to tuberculosis in all the cases, both tuberculous and nontuberculous, among those examined at the Dispensary during the three years of 1913, 1914 and 1915. Starting at first on the plan followed by many institutions of classifying the amount of exposure to tuberculosis among the tuberculosis patients, I extended the study to the equally large group of nontuberculous people visiting that clinic. I found, of course, quite an amount of family history of tuberculosis among the tuberculosis patients, as noted elsewhere, but was surprised, when extending the investigation to the nontuberculous patients, to also see similar results in that control group—and, in fact, an even greater amount of tuberculosis in the parental histories of the non-

tuberculous patients. The details of the 5,294 cases studied, which were practically equally divided between those having tuberculosis and those not having tuberculosis, are given in tables 2 and 3.

TABLE 2

*Exposure to infection in 2,785 tuberculous patients**

POSSIBLE SOURCES OF INFECTION	2,605 ADULTS		180 (a) CHILDREN		2,785 TOTAL TUBERCULOUS	
	Number	Per cent	Number	Per cent	Number	Per cent
Preceding generation (b)	306	12	75	42	381	*14*
Immediate generation (c)	289	11	22	12	311	*11*
Succeeding generation (d)	25	1	0	0	25	*1*
Consorts	132	5	0	0	132	*5*
Fellow employees	14	1	0	0	14	(e)
Contaminated houses	11	(e)	0	0	11	(e)
Source unknown	1,706	65	69	38	1,775	*64*
Several sources	122	4	14	8	136	*5*

(a) Children under sixteen years of age.
(b) Parents, grandparents, occasional aunt or uncle.
(c) Brothers, sisters, cousins.
(d) Sons, daughters, nephews, nieces.
(e) Less than half of one per cent.

* Compiled from the histories of every tuberculous case discharged at the Tuberculosis Clinic of Bellevue Hospital, New York City, during the years 1913, 1914 and 1915.

TABLE 3

*Exposure to tuberculous infection in 2,509 nontuberculous patients**

POSSIBLE SOURCES OF INFECTION	1,638 ADULTS		871 (a) CHILDREN		2,509 NOT TUBERCULOUS	
	Number	Per cent	Number	Per cent	Number	Per cent
Preceding generation (b)	212	13	552	63	734	*30*
Immediate generation (c)	159	10	102	12	261	*10*
Succeeding generation (d)	38	2	0	0	38	*2*
Consorts	125	8	0	0	125	*5*
Fellow employees	7	(e)	0	0	7	(e)
Contaminated houses	6	(e)	3	(e)	9	(e)
Source unknown	1,039	64	133	16	1,172	*64*
Several sources	52	3	81	9	133	*5*

* Compiled from the histories of all the nontuberculous cases examined at the Tuberculosis Clinic of Bellevue Hospital, New York City, during the years 1913, 1914 and 1915.
(a) For other footnotes see bottom of table 2.

Among 2,605 adults having tuberculosis, 306, or 12 per cent, gave a history of tuberculosis in the preceding generation, namely, in their

parents or grandparents, and occasionally in an uncle or aunt. Among 1,638 nontuberculous adults, 212, or 13 per cent, reported likewise the presence of tuberculosis in the preceding generation in their families. In other words, both tuberculous and nontuberculous adult patients examined from the East side of New York City had been equally exposed to tuberculosis from their parents. After all, it is exactly what we should expect, not only in a tuberculous group at that time but among the general population, since tuberculosis was then causing an average of 13 per cent of all the deaths in the district.

When, however, to the two groups of tuberculous and nontuberculous adult patients we added the number of children belonging to each respective group, a greater amount of tuberculosis in the preceding generation was found among the nontuberculous children than in the parents of tuberculous children. As a matter of fact, 30 per cent of all the nontuberculous cases reported tuberculosis in the preceding generation of their families, as against 14 per cent of the tuberculosis patients reporting the disease in their parents.

It is, of course, easy to roll up a large percentage of tuberculosis in a family history if one adds up the numbers relating to tuberculosis in the preceding, immediate, and succeeding generations. I believe that the best place to study the factor of inheritance is to be found in natural lines of descent instead of mixing collaterals and descendants that are greatly affected by infection or resistance after birth, rather than through inheritance.

PARENTAL HISTORY

After studying the frequency of exposure to tuberculosis, as disclosed by the ordinary method of history taking, I was interested in seeing the incidence of tuberculous disease found in patients according as to whether they were descendants of tuberculous parentage or descendants of nontuberculous parentage. Three series, totalling almost 7,500 cases examined between 1912 and 1916, were studied for these points. The details are given in table 4.

Among 1,577 cases with a positive parental history of tuberculosis, 540, or 34 per cent, upon actual examination were found to be tuberculous. Among 5,852 cases with a negative parental history, 3,463, or 59 per cent, were found tuberculous. In other words, there was a greater amount of tuberculous disease in the offspring of nontuberculous

parents than among the descendants of tuberculous parents. These results seem startling, but upon second thought not surprising. I first noted and reported (4) the results in a series of 714 cases so studied in 1912 at Bellevue Dispensary, when the percentage tuberculous among those with a negative parental history was found to be 70, as against 41 in cases with a positive parental history.

During 1913, 1914 and 1915 another series of 5,294 cases was gathered and the results show 58 per cent of tuberculosis among those with a negative parental history as against 33 per cent in those with a positive parental history. A third series of 1,421 cases studied in 1916 shows similar results: 60 per cent tuberculous in those with a negative history as against 34 per cent in those with a positive history.

TABLE 4

*Incidence of tuberculosis in 1,577 descendants from tuberculous parentage and in 5,852 offspring of nontuberculous parents**

GROUPS	PARENTAL HISTORY (a) POSITIVE (1,577 CASES)				PARENTAL HISTORY (a) NEGATIVE (5,852 CASES)			
	Offspring tuberculous		Not tuberculous		Offspring tuberculous		Not tuberculous	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
5,998 adults	432	*57*	321	43	3,327	*63*	1,918	37
1,431 children (b)	108	*13*	716	87	136	*22*	471	78
Total cases (7,429)	540	*34*	1,037	66	3,463	*59*	2,389	41

(a) Father, mother, or grandparent occasionally.

(b) Children under sixteen years of age.

* Compiled from the histories of cases discharged from the Tuberculosis Clinic of Bellevue Hospital, New York City, during the years 1912, 1913, 1914, 1915 and 1916.

The tubercle bacillus attacking the offspring of nontuberculous parents is seeking to implant itself upon practically virgin soil, as compared with its attacks upon the offspring of tuberculous parents who have been tried and who have already yielded a tuberculous crop. (The results are graphically shown in chart 1.)

This finding of a smaller amount of tuberculosis among the descendants of tuberculous parents has been duplicated elsewhere in a number of instances, if one would but note the similarity. Dublin (5), in his address in 1923 at Santa Barbara, stated that, according to the experience of the Metropolitan Life Insurance Company, "the children of the industrial population have lower rates for tuberculosis than exist

in the general population." He is also careful to add that among the industrial population itself the prevalence of tuberculosis is greater than in the general population. In our own opinion, it is because of the previous greater amount of tuberculization in the industrial population that there is a smaller amount of tuberculosis in their children.

So keen and competent an observer as Vincent Y. Bowditch (6) reported significantly upon similar findings in his own family. In his "Reminiscences," published in the *Journal of the Outdoor Life* in 1919,

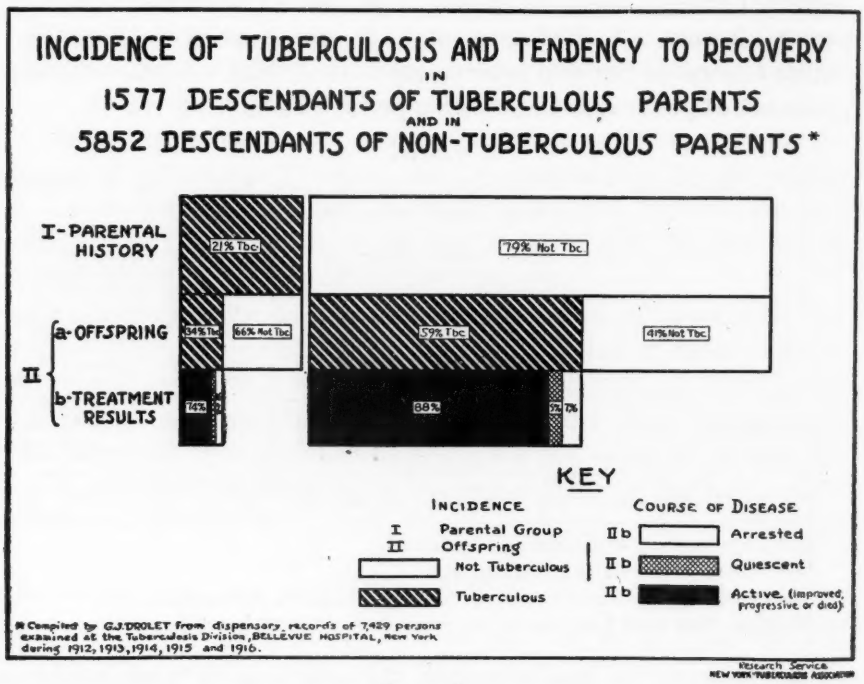

CHART 1

he said, in his recollections of episodes in the medical career of his father, Henry Ingersoll Bowditch, that, in a

> paper to be found in the *Transactions of the American Climatological Association* . . . . he (H. I. Bowditch) cites the case of his father (Vincent's grandfather), who, at the age of thirty-five, was seized with severe hemorrhages and with other symptoms of beginning tubercular disease of the lungs. . . . . He spoke of his father's removal to Boston; of his living to the age of sixty-five years; of his death from cancer of the stomach, and the discovery, after death, of the old healed lesion in his lung, which had been active thirty years before.

Having given the main facts of his father's illness, his apparent recovery, and his death from another cause, my father proceeded to give the interesting data that in spite of the fact that his father (Vincent's grandfather) had developed tubercular disease, and that his mother (his father's cousin) had died of fibroid phthisis ('old-fashioned consumption') yet none of their descendants—93 in number at the time of writing (1889)—had shown the least sign of tuberculosis in any form.

A footnote to the article adds: "In 1919, it may be recorded that, in a large and ever-increasing number of descendants, there has appeared no case of tuberculosis."—*V. Y. B.*

Why shouldn't there be greater resistance to the spread of tuberculosis into a disease condition where the stock has already been tuberculized? We know well what is called Koch's phenomenon. Opie (7) only recently described it again by saying "that a first infection with tubercle bacillus produces in a normal animal a progressive local lesion at the site of injection which quickly spreads to the nearest lymphatic nodes; whereas if the bacilli are again injected into an animal already tuberculous, the lesion . . . . will tend to heal." Why, then, should not we find likewise, in an already tuberculized group, a greater capacity for recovery or healing?

The study of inheritance in mental cases itself furnishes similar results. The Mendelian laws of heredity are now common knowledge. We know that in feeblemindedness, "when one parent is normal and the other is feebleminded, approximately 37 per cent of the offspring are feebleminded" (8). In other words, starting from stock that in the beginning was 50 per cent feebleminded, we have, in the succeeding generation, a reduction of the incidence of that condition to 37 per cent. This is not to argue that the processes and reactions against the tubercle bacillus are naturally similar or identical to the processes in the development of eradication of neuropathic traits, but the analogy and evidence of Nature's powers of resistance and recovery are to be noted.

TENDENCY TO RECOVERY

I was interested to follow further the course of tuberculosis in those developing active disease, according to whether they were descendants from tuberculous parentage or from nontuberculous parentage. The results of treatment in 1,218 tuberculosis patients, classified within these

two groups, were found to be more favorable if the patients were from stock with a parental history of tuberculosis than if descended from parents or stock not tuberculous in the preceding generation. Details of this study are shown in table 5 and are illustrated in chart 1.

Among two series of cases, one studied in 1912 and reported upon at that time (4) and another studied in 1916, covering in all 1,218 tuberculous patients, 16 per cent of those with a positive parental history became apparently cured or arrested cases of tuberculosis, whereas only one-half as many, or 7 per cent, reached a similar condition among the tuberculosis cases whose parental history was negative.

TABLE 5

*Results of treatment in 1,218 tuberculous patients from tuberculous parents and from non-tuberculous parents**

PARENTAGE AND CONDITION	STAGE OF DISEASE			Non-pulmonary	TOTAL	
	I	II	III		Number	Per cent
Parental History Positive (159 cases):						
Apparently cured or arrested	15	7	0	3	25	*15.7*
Disease quiescent	6	10	0	0	16	*10.1*
Improved, unimproved or died	42	53	17	6	118	*74.2*
Parental History Negative (1,059 cases):						
Apparently cured or arrested	52	20	0	2	74	*7.0*
Disease quiescent	26	20	3	1	50	*4.7*
Improved, unimproved or died	324	420	175	16	935	*88.3*

* Compiled from the histories of the tuberculous cases among patients discharged at the Tuberculosis Clinic of Bellevue Hospital, New York City, during the two years of 1912 and 1916.

Similarly, the results of treatment, as displayed by those reaching a quiescent stage in their disease, were twice as favorable among those with a positive parental history as among those with a negative history.

The after-history of "patients one or both of whose parents had consumption" has been studied by Karl Pearson himself through the investigation of Elderton and Perry (9) into the mortality of the patients treated at Trudeau Sanatorium. These observers in their interpretations of the findings at that institution concluded that, in their opinion, "it does not make much difference . . . . whether . . . . parents have consumption or . . . . not." But these excellent workers carefully appended their data to their report; and the results, in my opinion, are in the favorable direction we should expect. Elder-

ton and Perry, comparing the actual number of deaths of Trudeau patients with the expected mortality of people of similar age and sex in the general population, first found, among the 3,000 Trudeau cases studied, that the mortality of the sanatorium patients who, when admitted, were still in the incipient stage, was three times as great (3.0) as in the general population, and that the mortality of advanced cases similarly compared was ten times as great (10.2). But among incipient cases with a parent tuberculous the mortality rate was less, namely, 2.6 times that of the general population, or 13 per cent more favorable than in patients with negative history. We must remember, too, that they did not compare, as they should have done, just the cases having a tuberculous parent with those having nontuberculous parents, but, instead, they contrasted them with all incipient cases, regardless of parentage. As a matter of fact, when the comparison is properly made between these two groups of incipient cases, the ratio of deaths of sanatorium patients to those in the general population is 3.04 when the parents were not tuberculous, as against a rate of 2.56 when parents were tuberculous—or, in the latter case, 16 per cent more favorable, a very material and significant difference within a single generation.

Among the second stage cases—which, as is well known, constitute the bulk of those at Trudeau Sanatorium—the ratio of deaths of sanatorium patients to the general population was 10.2 times as great for the moderately advanced cases without tuberculosis in their parents, as compared with a ratio of 9.5 among those with a tuberculous parent, indicating again a mortality 7 per cent more favorable in the second group, even though the full benefit of the figures available for comparison was not utilized, as pointed out previously. For far advanced cases these authors were careful to state that there were very few of them, and that the differences brought out by comparisons might not be significant. In other words, American evidence handled by Pearson himself, the author of the phrase "inheritance of tuberculous diathesis," does not substantiate his statement in a group highly selected for tuberculosis and is not at all comparable to a more normal distribution as that of the Bellevue cases in New York City. Pearson must have felt the existence of some such possibility when he wrote in his noted pamphlet on *Questions of the Day: the Fight Against Tuberculosis*, as follows: "There is the question of hereditary immunity. It may be a bitter pill for mankind to swallow when we suggest that natural selection

may have done more for racial health in this matter than medical science, but it may have its compensations from the economic standpoint. Above all, it may suggest that Evolution helps man better than he knows how to help himself, and that possibly he would learn to help himself better if he studied her processes of racial selection a little more closely." (10)

This greater ratio of recovery from tuberculosis in patients whose parents have had tuberculosis has been noted by others—sometimes without the realization of its significance, but obviously with a respect for facts whether in accordance or not with their preconceptions. For instance, in a footnote of the first *Report of Gouverneur Hospital Tuberculosis Clinic*, New York City (11), I found the following statement in their study of cases treated between the years 1903 and 1910: "One other table of results, based upon a study of 218 cases, was submitted by one tabulator, and is of interest from another point of view. Of 75 cases with positive family history, 35, or 46.6 per cent, were unimproved, or progressive, or died. Of 143 cases with negative family history, 97, or 67.8 per cent, were unimproved, or progressive, or died. . . . . The cases studied included all deaths and patients under observation one month or more."

Philip (12), while himself apparently not a believer in the theory "of communal immunization on natural lines," nevertheless stated recently, when speaking of the declining death rate in England: "The comparison shows that, by some means or other, a successful resistance is now being offered to tuberculosis invasion which was not offered before." He also refers to Metchnikoff and others, who maintain that "a process of gradual immunization is in progress in thickly populated countries through natural vaccination."

Trimble (13), the Tuberculosis Officer of Belfast, Ireland, states, in his last report, that "the result of the re-examination of . . . . patients (Central Tuberculosis Institute, Belfast) has shown that in a large number of cases there is no need for further treatment, and, strange as it may seem, some of the *patients who have done best are those who have had family associations* with tuberculosis. Apparently these patients have benefited by an acquired immunity which, though they have become infected with tuberculosis, has enabled them to resist a fatal final issue."

TRANSMISSION OF IMMUNITY

How a greater resistance against tuberculosis in the offspring of tuberculous parents is acquired may be difficult to understand and to ascertain, but the facts available leave no room to deny its existence. Some light in this direction is, however, already shown through the work of laboratory observers. Ribadeau-Dumas, Cuel and Prieur (14) "found, by means of the complement-fixation test performed on tuberculous mothers and their infants, that women with open tuberculosis can transmit antibodies to the infant, but that the antibodies disappear from the infant's blood shortly after birth."

Stuhl, as quoted by Peterman (15),

> is of the opinion that, if the infant is not taken away from the tuberculous mother, the mother should nurse the child. He thinks the passage of antibodies from mother to infant by the milk has been proved by animal experimentation and that these produce a passive immunity. Daily examples of infants who have escaped infection when nursed by their tuberculous mothers also prove that the milk contains antibodies. The author believes, too, that the number of antibodies in the milk can be increased by treating the mother with tuberculin during pregnancy and lactation.

Certain autopsy findings also furnish evidence of the transmission of tuberculosis immunity. Robertson (16) of the Mayo Clinic, after studying the anatomic evidence of almost six thousand autopsies, says that "there is evidence that the increased immunity obtained as the result of a healed tuberculous lesion has been distributed to the succeeding generations."

This transmission of hereditary immunity has been equally noted in typhoid fever through animal immunization. Guyer and Smith (17) state that "antibodies pass to the young through the placenta, and this produces a more lasting immunity than the 'passive' transfer through the milk. 'Young of immunized mothers can without further immunization transmit agglutinating ability to their own offspring.'"

With the facts now before us of a decreased incidence of tuberculosis in succeeding generations which have been tuberculized and of a greater tendency for recovery in the descendants when attacked by tuberculosis, we can now understand better two great outstanding phases in the epidemiology of tuberculosis; namely, first, the present common experience of a decline in the tuberculosis death rate in most countries,

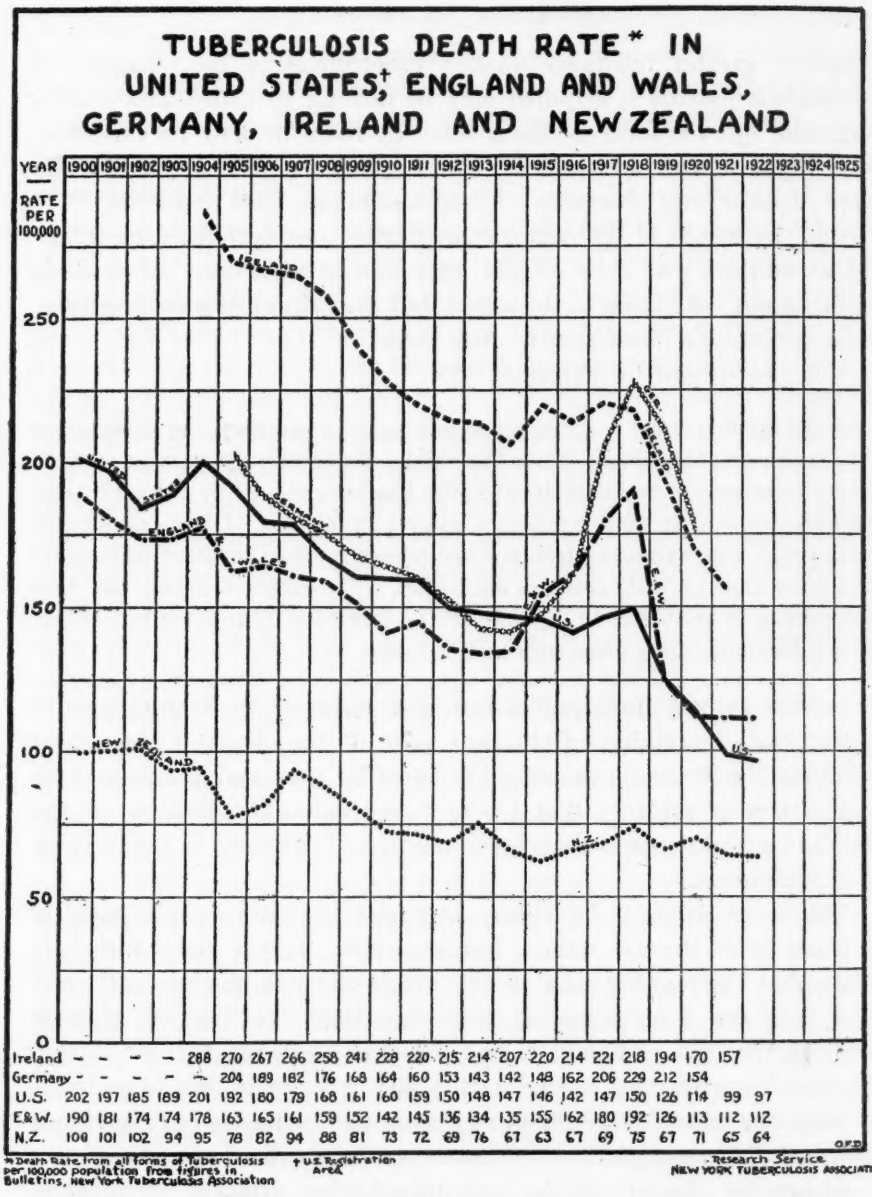

CHART 2

frequently starting even before the discovery of the specific cause of the disease, and in many instances independently of definite anti-

tuberculosis work; second, the admitted and widespread difference in the incidence of tuberculosis in various racial stocks, and especially the greater resistance in the groups that have been tuberculized longer than others. (See charts 2 and 3.) The present lesser and decreasing amount of tuberculosis among the Jews, the Italians and the English, all stocks that have known town and city life longer and a greater amount of infection than among, for instance, the descendants of agricultural stocks, or of those living formerly in the open air, like the Irish,

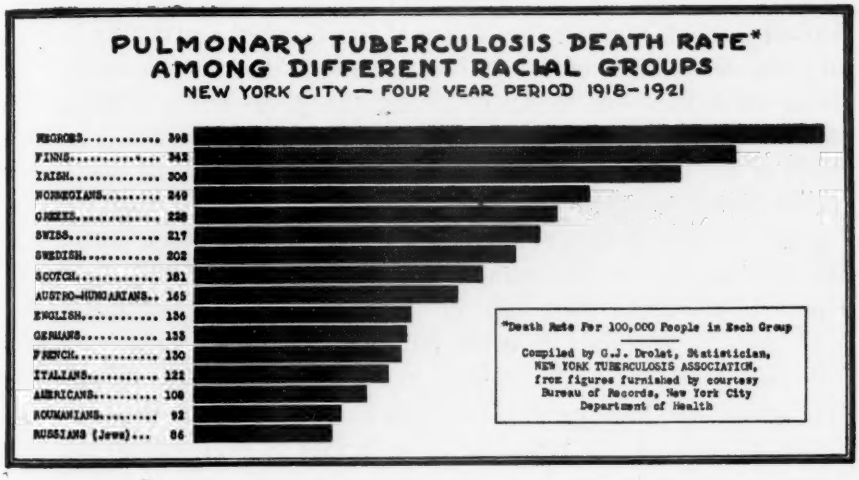

CHART 3

the Scandinavians, the Negroes and the Indians, can also be better understood. If, in a single generation of passing through tuberculosis a difference may be noted in the offspring, much of the progress made against this epidemic among those first mentioned above undoubtedly has been made, in a measure as just indicated. Immunity against tuberculosis is being acquired just as it has been secured in many other infections now relegated to simple childhood infections, though these diseases would be fatal in nonimmunized primitive races.

While we are compelled to admit the importance of the inheritance factor in tuberculosis as one of those that Nature utilizes for her own advancement, and as one making for steady progress, we must be aware that it is a painful and expensive, if not frequently life-costing, mode

of acquiring immunity. We must not in the least undervalue or ignore the full importance of the gains that may equally and more readily be obtained through modifications of environment, betterment of living conditions and through improved changes by education in personal hygiene and all that the public health movement stands for.

The slow gain through evolutionary progress does not begin to compare with the tremendous progress made, frequently in less than a generation, in the fight against tuberculosis, especially in this country. In New York City itself, where some of the benefits against tuberculosis derived through heredity are obvious, I found, when contrasting in that city the death rates of the different sections, that the importance of living conditions—for instance, among the Jews—made striking differences in the incidence of that disease. As already reported in Bulletins of the New York Tuberculosis Association (18), the death rate of the Jewish people in the lower East side or Ghetto section was the highest for that group anywhere in the city, whereas when portions of the older generation and younger elements moved into the better tenements of the upper East side, or again into the new law tenements, with their air and light in every room, in the Bronx, their death rate fell steadily and markedly. Again, in the Brownsville section of Brooklyn, where the Jews have found individual homes and freedom from tenement dangers, the tuberculosis death rate in 1921 was 50 per cent lower than that on the East side during the same year, and as low as that of Framingham itself.

Both environment and heredity affect tuberculosis mortality. What is called heredity to-day is but the result of the environment of yesterday. These lie largely within human control. But there is necessity for a more correct understanding of the importance of the factor of inheritance in tuberculosis. It may even be enlisted along with other means of improvement. Inheritance in tuberculosis is not in the direction of a predisposition to the disease, but towards the acquirement of immunity itself.

SUMMARY

1. "Family histories of tuberculosis" have generally been gathered from institutions where the patients were almost exclusively of that type and hence have lacked control figures similarly gathered from the general or normal population.

2. More secondary cases of tuberculosis should be expected in families in which one individual has already been attacked than in other families, as the opportunities for infection as well as the living or working conditions are more nearly alike within the same family group.

3. At Bellevue Dispensary, in New York City, among 1,695 children tested with tuberculin, no greater amount of tuberculosis was found among children with tuberculous parents than among children from normal parents. The reaction was positive in 64 per cent of the first group and in 66 per cent of those in the second group.

4. Exposure to tuberculosis was found to have been reported more frequently among nontuberculous patients than among those who were tuberculous. Among 2,509 nontuberculous cases 30 per cent gave a history of tuberculosis in one or both of their parents, whereas among 2,785 tuberculous patients only 14 per cent reported a parental history of the disease.

5. When tuberculosis attacks offspring from nontuberculous parents, a greater toll is taken than among those descended from tuberculous parents. In the first group the bacillus is implanting itself in virgin soil; in the second, it finds greater resistance. Among 5,852 persons with a negative parental history, examined at Bellevue, 59 per cent were found tuberculous; among 1,577 members, with a positive parental history, only one-half as many were found tuberculous, namely, 34 per cent.

6. There is a greater tendency to recovery from tuberculosis in patients descended from tuberculous parents than in individual members of families attacked for the first time. In 118 tuberculous cases with positive parental history, 26 per cent reached a stage of quiescence or arrest of their disease, whereas in 1,059 patients with a negative parental history less than half, or 14 per cent, reached such a condition of arrest or quiescence of their disease.

7. The almost universal decline of tuberculosis in countries or communities where it was formerly epidemic, and the decreased incidence of this disease in racial stocks that have been exposed longer to urbanization and to tuberculization, have in a measure been due to an increasing immunity acquired by hereditary evolution.

8. Children of tuberculous parents do not inherit even a predisposition to the disease, but an increasing degree of immunity to it, instead.

9. The progress against tuberculosis through heredity is slow, and frequently life-costing. It is greatly hampered, and, at times—as during wars or periods of scarcity—even obscured by unfavorable general conditions of life. Betterment of social conditions, modifications of personal life, especially through education, yield far greater gains and a fuller assurance of an ultimate complete control of the disease.

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THE RESULTS OF PIRQUET TUBERCULIN TESTS ON 1,654 CHILDREN IN A RURAL COMMUNITY IN MINNESOTA[1]

S. A. SLATER[2]

It has become a habit with most of us to quote statistics showing that from 60 to 90 per cent of all children are infected with tubercle before they reach the age of fifteen. This idea has been derived largely from reports on the results of the Pirquet tests made, for the most part, in the clinics of the larger cities, notably Vienna, Berlin, Lille, New York and other large centres of population. Naturally, most of those who resort to these clinics do so either because some member of the family has tuberculosis, or the children are from the poorer districts and the clinic is the only means they have of obtaining medical attention. The result, under such conditions, is not a fair means of arriving at the percentage infected even for the city in which the tests are made. In other words, a few hundred children tested from the class most apt to be infected would not give one a fair estimate of the number infected in a city of several million people. It would be even more unfair to feel that the smaller towns and rural communities, where living conditions are better, should also show as high a percentage. In the reports of children from the better families who have been tested, these were reached by the physician because some member of the family had the disease. Results under these conditions were likewise high, as was to be expected. In order to get a fair estimate of the number infected in any city or community it is necessary that children be selected so as to represent the entire population.

It can be readily seen that it would be practically impossible to do this if the tests were given in the clinic or in the offices of physicians where only the children of the latters' patients were available. It would therefore seem that the practical way to obtain a fair result would be to take

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the test to the child. This can be done by selecting homes in different parts of a city or community and giving the tests there, or it might be done in the schools representative of the city or district. The former method would make the task too great; the latter would not make it possible to get children under six years of age, and it might also be difficult to get the consent of the school authorities.

Feeling that we had been too prone to cite statistics stating that the majority of all children are infected before they reached the age of sixteen, and that this condition does not exist throughout the country, led us to do the work presented in this paper. It is not my intention to claim that the percentage of infection is actually as low as shown here, for that would be as misleading as to quote statistics compiled in the cities where infection is high, in order to show that it is the same everywhere. It is only natural that a study of this sort, conducted in what is considered a wealthy farming section where the death-rate from tuberculosis is about 35 per hundred thousand, where living conditions are good and the people intelligent and willing to coöperate in helping to lower the death-rate, should stand at the other extreme. Obtaining the extremes, however, should help us arrive at a reasonable medium.

In conducting this study every effort was used to make it accurate and, at the same time, as representative of the existing conditions as possible. As a precaution to insure accuracy it was done by one man with the assistance of nurses. The tests were given by the physician who also interpreted the results forty-eight hours later. Koch's old tuberculin, human type and undiluted, was used, and only two scarifications were made on the forearm, one for the tuberculin and the other for the control. The scarifications were from one to two inches apart, the upper being used for the test and the lower for the control, thus avoiding any danger of the lymphatic circulation taking the tuberculin to the upper spot, had the operation been reversed, and thus cause a reaction in both. Some have preferred to use three scarifications, the one in the middle being the test and the ones above and below being controls. I could not see the advantage of this if one is certain to use the upper for the test. Two scairfiers exactly alike were used, one for the tuberculin and the other for the control, thus avoiding the risk of having tuberculin on the latter, should it not be thoroughly cleansed at the time it was used for the control.

Schools were used, since we thought that they would provide the best means of reaching the children representing average conditions through-

out the district. To conduct the test in the home would possibly have been more satisfactory, in that children under six could have been obtained, but this would have entailed too much work. Having the children brought to the sanatorium, to be tested, was thought of, but abandoned because only the children of parents in the institution or those of their friends would avail themselves of the opportunity and thus comprise mostly those who had been exposed. The result would then be unfair for the district as a whole, in that the number reacting would be larger than the average for the district. Had clinics been conducted and those tested asked to return two days later, many, especially those who reacted, would not return for observation. In this instance the result would again be unfair, since the percentage of reactors would appear smaller than it should be. In using the schools I believe the fairest means possible was made available. It was not compulsory that a child take the test, but most of them did; and in some schools all submitted to it. The results in the schools where all took the test and in those where only a part took it were practically the same, showing that those who did not take it were not more likely to be infected. A card was filled out for each child on which as much of the history as was possible to obtain was recorded. Two days after giving the test the school was again visited and those children found with positive reactions were given physical examinations. If the test was negative no further examination was made unless it was specially indicated, and the test was not repeated. It might be mentioned that in a number of cases a second test was given, with the result so nearly the same as the first that it was given up, as we came to feel that one test was sufficient for practical purposes. Schools in the different parts of the four counties in which the work was done were used. Some of these were in the larger towns, none of which were over 3,500 population, others in the smaller towns and villages, and others in the consolidated and one-room schools in the country. Schools representative of the entire district were selected varying in the number of pupils from eight or ten to several hundred and in buildings that were not modern to those of the best construction. The number of children tested was sufficiently large to give a fair estimate of the percentage infected throughout the counties in which the work was conducted.

The general result was as shown in table 1.

Those grouped under the first heading were the ones who had not been exposed to any known case of open tuberculosis. This accounts for the

small number reacting. Under the second heading were placed all who were not sure they had not been exposed and also those for whom no history of exposure could be obtained. More than half were placed under this heading for the latter reason and it should probably read "doubtful history" rather than "history of doubtful exposure." When considered under the latter a large number of reactions might be expected, but when considered otherwise the reason is evident why the percentage was low. Under the third heading were placed those known to have lived in a home with an open case of tuberculosis. The percentage reacting

TABLE 1

AGE	NO HISTORY OF EXPOSURE		HISTORY OF DOUBTFUL EXPOSURE		HISTORY OF KNOWN EXPOSURE		TOTAL	POSITIVE	NEGATIVE	PER CENT POSITIVE
	Positive	Negative	Positive	Negative	Positive	Negative				
5 and under	1	39	6	44	5	5	100	12	88	12
6	3	34	6	82	4	1	130	13	117	10
7	1	42	7	106	2	1	159	10	149	6
8	2	41	9	93	4	1	150	15	135	10
9	4	47	7	92	7	0	157	18	139	11
10	0	58	15	103	6	1	183	21	162	11
11	3	60	8	82	4	0	157	15	142	9
12	5	47	9	79	3	1	144	17	127	12
13	1	46	10	60	3	0	120	14	106	12
14	3	50	6	53	7	0	119	16	103	13
15	3	39	1	43	3	2	95	7	84	7
16 and over	4	30	4	100	5	1	414	13	131	9
Total.....	30	533	88	937	54	13	1,654	171	1,483	10
Per cent positive.....	5.3		8.6		81					

under this heading might seem unduly large in view of the fact that the others were so small and it would have been much smaller if all those with a family history of tuberculosis had been placed in this group rather than only those known to have been exposed.

It is rather appalling to think that 80 per cent of all children living in homes where there are open cases of tuberculosis are infected, even when these surroundings are as nearly ideal as might be found anywhere. This circumstance surely emphasizes the fact that it is practically impossible for a child to live in a home with an open case of tuberculosis without becoming infected, especially when the patient had not been instructed

to take the proper precautions to prevent the spread of infection. It is interesting to note the slight differences in the percentages reacting for the different ages. It is generally supposed that the older the child the more likely he is to react. It would seem from the above table that a child exposed to a small amount of infection would be able to take care of it without having an allergy created. When one is being constantly infected or receives massive doses, as occurs in the home with an open case, one will be sure to react. The reason for the higher percentage of positives among those under five years of age is explained as due to the fact that a number of children were brought in to be tested because it was thought that they had been exposed.

TABLE 2

AGE	LYMPHATIC INVOLVEMENT	LUNG INVOLVEMENT	LUNG AND LYMPHATIC INVOLVEMENT	PHYSICAL FINDINGS NEGATIVE	TOTAL
5 and under	9		1	2	12
6	10			3	13
7	8			2	10
8	14			1	15
4	12		2	4	18
10	18	1		2	21
11	13			2	15
12	9	2	2	4	17
13	8	1		5	14
14	9	2	2	3	16
15	4	1		2	7
16 and over	1	3	2	7	13
Total.....	115	10	9	37	171

Table 2 shows lymphatic and lung conditions in those reacting positively, as these were determined by physical examination. It is interesting in that the younger children showed more lymphatic involvement while, with increasing age, lung involvement or both lymphatic and lung involvement became greater.

Table 3 shows that the percentage of positive reactions among boys and girls varied only slightly, the difference being less than 2 per cent. While the number is too small to draw a significant conclusion it is interesting to note that under six years the percentage of boys reacting positively was higher, while from six to nine the girls were higher and from ten to fourteen the boys again led. It might be expected that the percentage of girls reacting positively would be the higher, for they are more closely confined.

Having given the test to over 1,600 children, I am thoroughly convinced that it is reliable. This is certainly true when the child has been exposed to massive infection or to a slight contact over a prolonged period. I am, however, of the opinion that a child living as most children do in this community can take care of a small amount of infection and, after a short period, not react. This would account for the fact that the older children do not show a higher percentage of positives.

While the result of this study may, no doubt, be surprising to many in that the percentages of positive reactions were so small, I believe that

TABLE 3

Reactions according to sex

AGE	MALE		FEMALE	
	Positive	Negative	Positive	Negative
5 and under	7	44	5	44
6	4	58	9	59
7	3	70	7	79
8	6	64	9	71
9	4	68	14	71
10	13	78	8	84
11	7	64	8	78
12	9	55	8	72
13	5	45	9	61
14	93	43	7	60
15		51	4	33
16 and over	4	55	9	76
Total.....	74	695	97	788
Percent positive.....	9		11	

a similar study in other localities where conditions are comparable would result not much differently. I am not able to compare the above results with those of other work of this kind in a rural community because I can find no report of any. Ferguson (1), of Saskatchewan, tested 1,346 cases in the towns and rural districts of the Province with the result that he found 56.6 per cent reacting positively at fourteen years of age. Some of the towns in which his work was done had a population of 40,000, and I do not feel that conditions in the rural communities of Saskatchewan are nearly so good as they are in Minnesota. Included also in Ferguson's report were 162 Indians who showed positive reactions in 92.5 per cent.

As stated in the beginning of this paper it is to be expected that a wealthy rural community, which has a low death-rate for tuberculosis, would naturally stand near the bottom in the percentage of children infected. It is quite evident that we have been accustomed to put the number infected with tuberculosis at entirely too high figures, and when the country as a whole is considered I doubt very much whether the percentage reacting positively would be more than half that usually given. In preparing this paper I have hoped that it may stimulate interest and further study along similar lines, in order that we may gain a better idea of the number infected in rural communities and throughout the country as a whole.

CONCLUSIONS

1. In a rural community, in which economic and hygienic conditions are unusually good, the percentage of children infected with tuberculosis is extremely low and suggests that, for the country as a whole, the figures cited are much too high.

2. In this community the percentage of positive reactors was not found to increase with advancing age. This circumstance may be due to the fact that many infections of early childhood have been relatively light and have thus not persisted and kept up the ability to react.

3. Under ordinary conditions every child in a home with a case of open tuberculosis becomes infected.

REFERENCE

(1) FERGUSON: Tr. Nat. Tuberc. Assoc., 1922, xviii, 330.

OBSERVATIONS OF ANNULAR SHADOWS AND CAVITIES AT THE CINCINNATI TUBERCULOSIS SANATORIUM[1]

KENNON DUNHAM AND VERA NORTON

In 1918, Sampson, Heise and Brown (1) called the attention of the National Tuberculosis Association to pulmonary and pleural annular radiographic shadows. They said,

A manifestation that leaves one in much doubt as to its diagnostic value in relation to intrapulmonary cavity is the annular or ring-like shadow, varying in shape, seen many times in the normal or mildly infiltrated lung fields, and it is this picture that we have attempted to investigate. Many times more ray is absorbed inside these annular shadows than in the surrounding lung tissue; in a small percentage of cases more ray is transmitted through this ring, while in about 60 per cent of the instances the transmission is the same. Lung markings are profuse in many of them even when the size is extreme, occupying an entire apex or upper third. The profusion of lung markings, the greater or equal absorption of ray through these annular shadows and also the fact that certain of them change their shape and size rapidly, make one very skeptical as to their value in the diagnosis of intrapulmonary cavities. (In many instances some as large as 3 to 5 cm. disappeared in from three to six months or became larger and then smaller and then finally disappeared.) This study of 50 cases, unselected from a much larger number, has led us to conclude that annular shadows, surrounding areas of increased or equal absorption of the ray, occur in patients more likely to be suffering from pulmonary softening and indicate rupture of the lung. Owing to the presence of adhesions only partial pneumothorax, with or without fluid, results.

In 1921 Amberson (3), (5), also before this organization gave another possible explanation of this same appearance saying, "The development of most pleural annular shadows indicates simple subacute or acute pleurisies."

Again in 1923 the subject was brought before this Association by Philip King Brown (7). He, in closing his paper, stated that he had "never yet found an annular shadow which was not shown to be a

[1] Read before the clinical section at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 7, 1924.

cavity." He called attention to the grave danger to the patient if cavities were mistaken for annular shadows.

Our reason for prolonging this discussion is that, though to the members of this Association the correct interpretation of these lesions may be of only academic importance, nevertheless to many victims of tuberculosis this differentiation means life or death.

It is important to differentiate between annular shadows caused by localized air-pockets or pleural changes and annular shadows due to cavities, because thin-walled cavities suggest a very grave prognosis and necessitate collapse of the lung. This danger is out of all proportion to the clinical signs and symptoms of the patient. Extensive tuberculous pneumonia and tuberculous caseous bronchopneumonia are frequently caused by the aspiration of infectious materials from cavities. This is especially true of thin-walled cavities. In such cases the disease spreads in spite of the usual rest.

In our experience the best method of making this differentiation is by means of artificial pneumothorax. This is practically without danger if we are dealing with an air-pocket and it is the treatment of choice if we are dealing with a cavity.

In our experience the vast majority of annular shadows have been proved to be due to cavity. In only one case have we evidence supporting the theory of pneumothorax as a cause of annular shadow.

Men in different laboratories throughout this country are referring to annular shadows. I have found very little uniformity of opinion as to what X-ray findings constitute an annular shadow. The original description of Sampson, Heise and Brown is not so helpful when dealing with the plate as one might expect from the clarity of their English.

To clarify the subject we must keep in mind annular shadows due to pneumothoraces (air-pockets) and pyopneumothorax, annular shadows due to pleural changes, and annular shadows due to pleural changes and thickened septa between the secondary lobules extending into the lung from the pleura. Distinct from these but confused in the minds of some are Barlow's (4) air-pockets and localized pneumothoraces (as at an apex) which do not produce annular shadows.

Another confusing picture which is most commonly seen at the bases is a pear-shaped (not annular) decreased density surrounded by a very delicate wall of increased density. This cannot easily be confused with annular shadows. We have confused it with Barlow's air-pockets.

One such case is presented in our autopsy series. Large emphysematous blebs were the cause in this case.

At autopsy we have been able to prove that cavities can cause annular shadows; also, we have been able to prove that the physical signs and X-ray plates of large cavities can so simulate pneumothorax that the differential diagnosis could only be cleared up at postmortem.

We have evidence by X-ray, by physical examination and by subsequent history that pyopneumothorax may be so localized as to simulate cavity. From this it can be reasoned that air-pockets may produce annular shadows or Barlow's pneumothoraces. Nevertheless, we have no postmortem evidence that either annular shadows or Barlow's pneumothoraces have been caused by air-pockets. Further, we have no postmortem evidence that either pleural change or pleuroseptal changes produce annular shadows. All annular shadows proved by autopsy have been found to be caused by cavities, and a suspected Barlow's pneumothorax to be due to an emphysematous bleb. These statements are made after a careful search which has lasted since the original papers were published (2).

We do not wish even to suggest that our studies prove that any of the explanations suggested as the cause of annular shadows or of Barlow's air-pockets have no pathological basis. We only report our findings. But we do believe that so much evidence of cavity and so little evidence of air-pockets should cause the diagnostician to go slowly when deciding that air-pockets rather than cavity are the cause of annular shadows.

Our effort has been to find a method which would differentiate between annular shadows due to air-pockets or pleural changes and annular shadows due to cavity. We have studied this problem by means of physical signs, X-ray, autopsies and induced pneumothoraces.

Physical signs cannot be depended upon. They may be present when cavity does not exist. They may be absent when cavity is known to exist. We have proved both of these statements by autopsy. A study of physical signs over cavity is another problem to which we have given much attention.

X-ray studies over a considerable time have frequently convinced us, but this is very slow and has too often led to bad results. Since last year we have tried oblique and transverse exposures as suggested by Brown and Burnham (6) (7). They are helpful but not always convincing.

Autopsies are not done as a therapeutic measure. Knowledge thus gained is for the other patient and medical advancement. The earliest possible answer must be had. The patient's life depends upon it.

The procedure which we recommend is induced pneumothorax. In this way we see the pleura stripped away from the chest wall, or held to the wall by adhesions and the cavity moved with the lung. The only dilemma after such a procedure which might exist is when the cavity is near the *incisura* and may be due to an air-pocket. We have had no such case, but expect that an air-pocket would change its shape more than a cavity.

Thus our diagnosis and treatment go hand in hand and no time is lost. If the lung cannot be collapsed for diagnosis, it cannot be collapsed for treatment, and again no time is lost.

We believe that there is only one case of annular shadow studied by either of us which could have been due to pneumothorax. That is included in this report. We have kept an open mind to every question which has occurred to us.

We present here only the cases which we have studied in 1923. Many of these have been seen before 1923 and most of them since 1923. We hope that this will give a clear cross-section of our work. We include such cases as we believe might have been mistaken for annular shadow due to pneumothorax, and these include three large cavities which simulated pneumothorax.

We wish to repeat what all of you have known for many years, that we never know which lung may be collapsed until we have tried. We report cases here which were successfully collapsed long after extensive pleural effusion had been removed, and the X-ray plates showed thickened pleura from apex to base and the diaphragm attached to the chest wall.

We present 67 cases;[2] 23 were annular shadows proved by pneumothorax to be cavity; 1 was an annular shadow so far proved by collapsing the lung, etc., to be due to pneumothorax. The annular shadow could not be seen after the collapse. This is a comparatively recent case and the annular shadow may return. This lesion was in the apex of the lower lobe. Over this lesion we had coarse moist râles, increased after cough, limited to a localized area and simulating exactly the signs found over our other lower-lobe lesions.

[2] Protocols of cases and autopsies referred to above are published in the *Transactions of the National Tuberculosis Association* for 1924.

Twenty-one of these cases are under treatment; 16 inside and 5 outside of the Sanatorium. Pleural effusion developed in 6; one was extensive with severe reaction. The fluid has absorbed and the lung is expanding. No annular shadow remains. In two the fluid seemed to be beneficial and assisted in completing the collapse. In three the fluid was negligible. One of these cases has died of general tuberculosis.

Thirty-two were annular shadows proved to the satisfaction of our entire staff to be due to cavity by X-ray studies over a long time. Many of these have changed position and size. It can be argued that we are biased. We can only reply that we have given each case careful study and have reported as honestly as we know. It is in this series and our postmortem cases that we have seen the ill effects from thin-walled cavities. Also, in this series we have seen some wonderful recoveries. Certainly all cavities should be collapsed whenever possible.

Eleven autopsies are presented. These include 6 annular shadows proved to be due to cavity. Two cases had very large cavities which simulated pneumothorax with massive destruction of both lungs; two had very large cavities which simulated pneumothorax with massive destruction of one lung; one had a large cavity simulating pneumothorax over the upper left lobe and an annular shadow in the upper right lobe.

Each of these 67 cases had positive sputum. All but four had one or more annular shadows on the X-ray plate. An area of decreased density surrounded by an area of increased density was noted. All of the lesions in the lower lobes were confined to the upper third of the lobe. Physical signs were frequently and carefully studied and noted. It is interesting that in only one case in which cavity existed in the upper third of the lower lobe is there any note on the chart suggesting cavity.

The only physical sign which seems at all constant over these lower-lobe cavities is moist, usually coarse râles, increased after cough, and limited to a circumscribed area. These râles are usually coarser than those heard over other lesions in the same chest.

The annular shadows found in the cases proved to be cavities by pneumothorax and at autopsy were located as follows:

	PROVED BY PNEUMOTHORAX	PROVED BY AUTOPSY	TOTAL
Upper right	6	3	9
Upper left	8	1	9
Upper lobes			18
Lower right	5	1	6
Lower left	4	1	5
Lower lobes			11

The large percentage of cavities found in the upper third of the lower lobes, as shown by these figures, is only a cross-section of what we have observed for many years. To us these findings indicate that these lesions are more common than is generally appreciated.

The quotation in the introduction of this paper refers to annular shadows "seen many times in the normal." We wish to state that neither of us has ever seen an annular shadow in what we call a normal chest. One of us has made a careful study of many hundreds of normal chest plates, both of children and of adults.

It is true that these statistics are taken from a Sanatorium for far-advanced patients. During 1923, 287 cases were discharged, of which 171, or 59 per cent, were far advanced. We had 136 deaths to 431 admissions in 1923 and autopsied 52 per cent. Whenever possible, the lungs have been taken out with the parietal pleura attached, so that we may search for air-pockets.

These facts may explain why we have not found what others have seen; but, again, one of us has had extensive experience at Oteen, North Carolina, during the war, has surveyed several Veterans Bureau Hospitals since then and has had an extensive private practice, and his observations differ very little from what these figures show.

We, therefore, believe that this report shows beyond a doubt

that most annular shadows, as we understand them, are due to cavity;

that most annular shadows due to cavity have thin walls;

that thin-walled cavities are a very serious menace to life;

that the patient can only be made safe by their collapse;

that the best means of diagnosis is by inducing pneumothorax;

that we are fortunate when we have a safe diagnostic method which is the treatment of choice;

that it is a great mistake to view annular shadows lightly;

that all of our cases had positive sputum;

that cavities in the upper third of the lower lobe are common and usually thin-walled, simulate pleural changes, are very dangerous and require collapse of the lobe.

The quotation in the introduction shows also that Sampson, Heise and Brown did not view these cases lightly. Their cases also had positive sputum and did not do so well as other similar cases. Our collapsed cases have done unusually well.

We regret that there has sprung up throughout the country a disregard for the gravity of annular shadows. We recommend that pneumothorax be induced to differentiate the causes of all annular shadows in cases having positive sputum. In this manner the proper treatment of the case can be determined and prosecuted.

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(3) AMBERSON, J. B., JR.: Theoretical explanations of the formation of roentgenographic pleural annular shadows, Ibid., 1921, p. 108.

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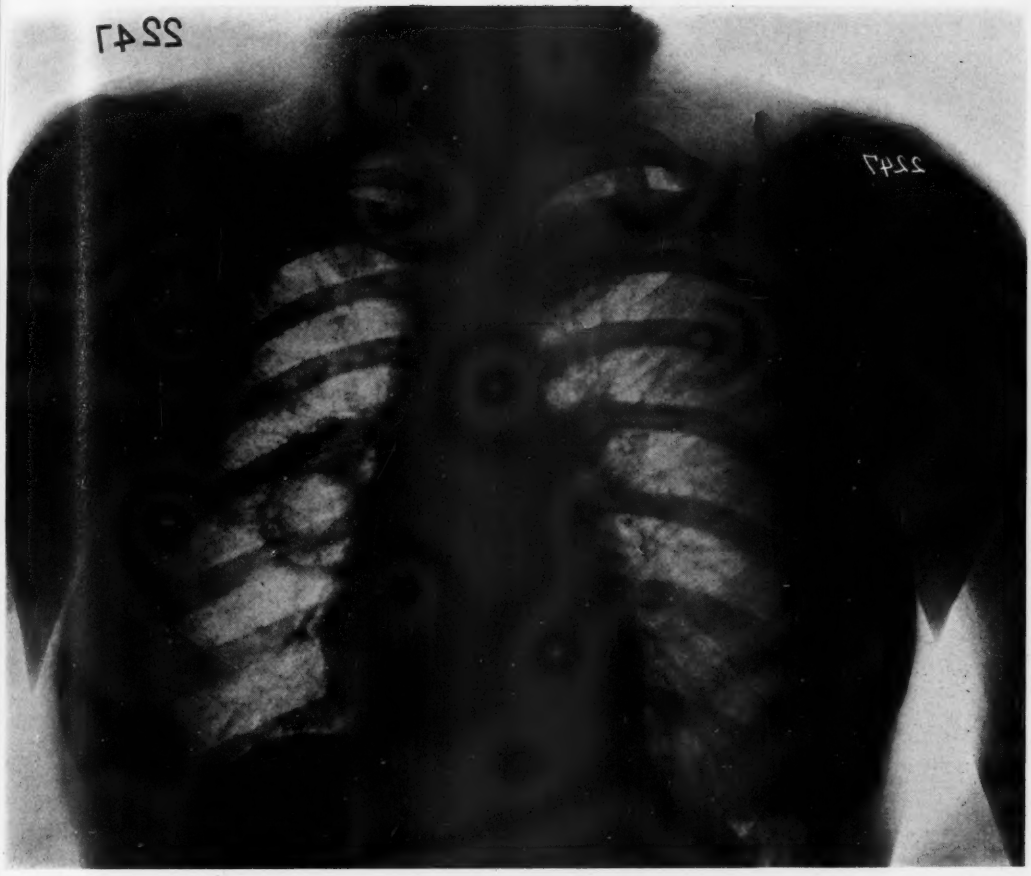

FIG. 1. CASE 4. G. G. NO. 2247. LARGE ANNULAR SHADOW UPPER PART LOWER RIGHT LOBE, EXTENDING FROM SEVENTH RIB TO EIGHTH INTERSPACE

CASE NO. 4. G. G. SEE FIGS. 1, 2 AND 3

Had a history of a severe right-sided pleurisy. Also had several small hemorrhages. Profuse râles were heard over right middle and lower lobes and plates no. 2247 (fig. 1), taken May, 1921, show a large annular shadow in upper part of lower right, coming to the surface to the right of the spine, immediately in front of the seventh rib and eighth interspace. Plates no. 2247B (fig. 2) were taken after the first collapse, 400 cc. having been given. The annular shadow is now proved to be definitely two cavities in the lower lobe with possibly a smaller one below.

Plates 2460 (fig. 3), taken after the ninth treatment, three months later. The lung is well collapsed, although the cavities are still seen. The case was discharged two years after beginning treatment but returns for compression. Just before the 47th treatment, a plate was taken on expiration and then one on inspiration. Neither shows any evidence of cavitation. The plate taken on expiration shows the trachea in the midline, lung collapsed, diaphragm behind the breast, heart almost to the left lateral wall, lung markings on the left not clear, left diaphragm not made out. The plate taken on inspiration shows the trachea to the right, extension of the lung far into the right thorax, right diaphragm far below the breast, heart to the right and in an almost perpendicular direction, lung markings on the left side clean-cut. The patient is doing well; is still treated about once a month.

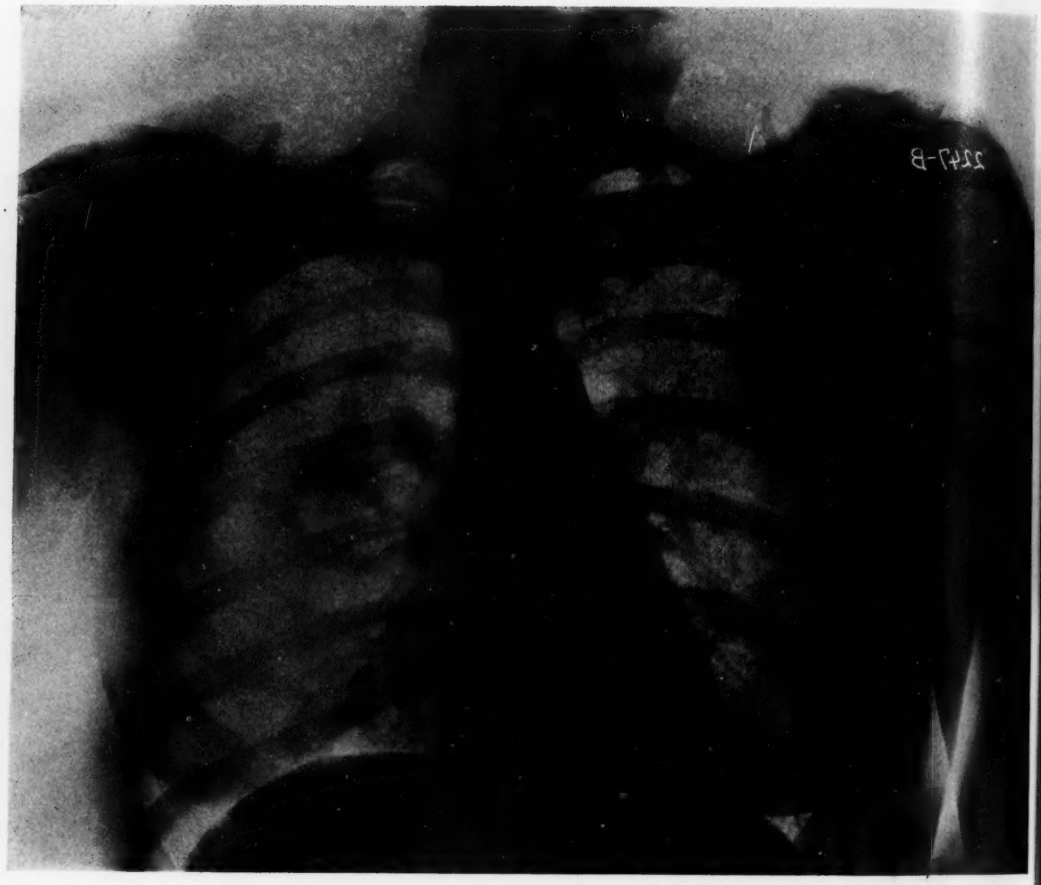

FIG. 2. CASE 4. G. G. NO. 2247B. SAME CHEST AFTER FIRST COLLAPSE. CAVITY MOVED TO RIGHT. HEART DISPLACED

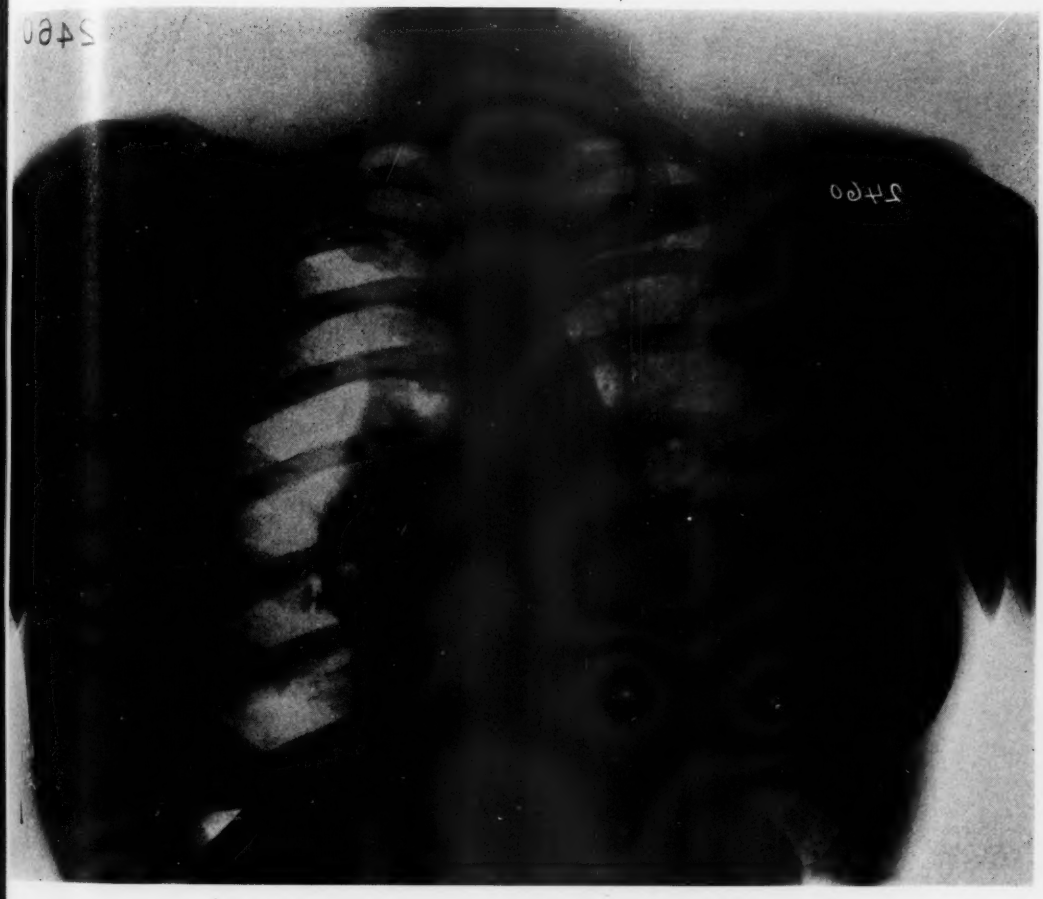

FIG. 3. CASE 4. G. G. NO. 2460. AFTER NINE MONTHS, THREE MONTHS LATER. LUNG MORE COLLAPSED BUT CAVITY STILL SEEN

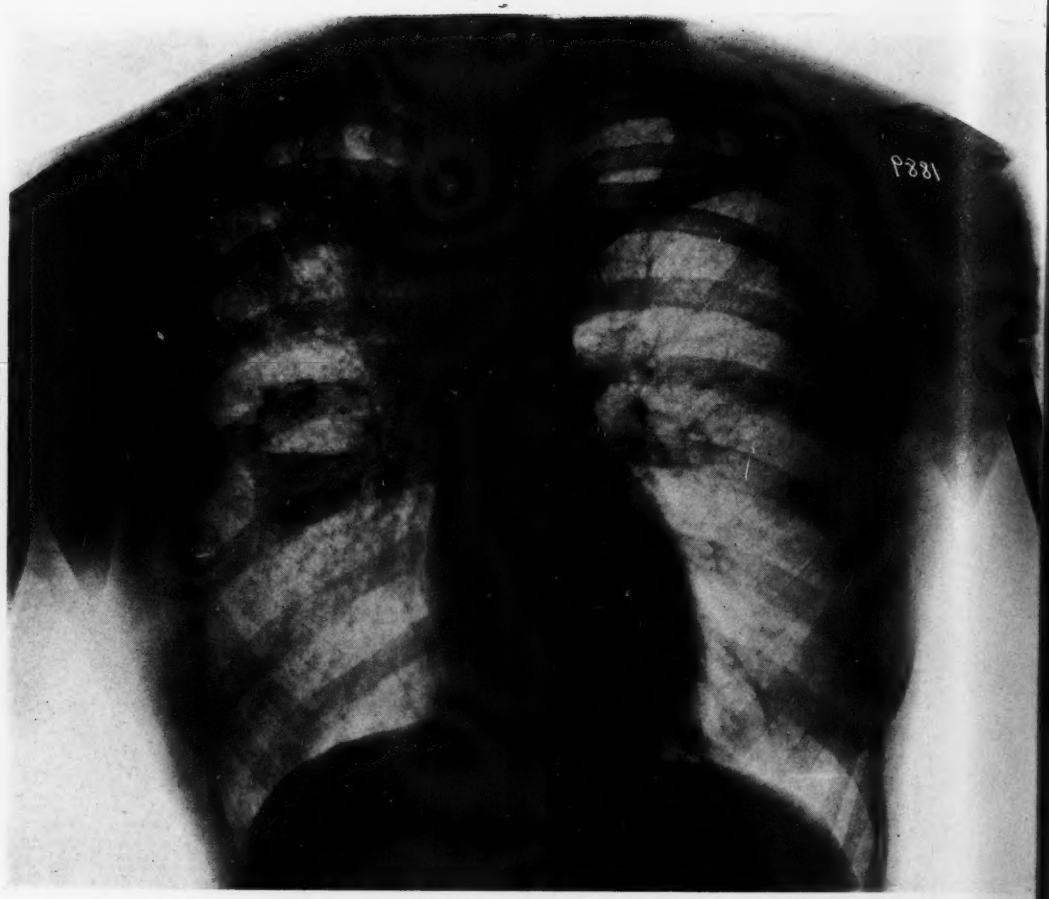

FIG. 4. CASE 10. L. W. NO. 1889. ANNULAR SHADOW, RIGHT SIDE, IN FRONT OF SEVENTH RIB, SHOWING FLUID LEVEL

CASE NO. 10. L. W. SEE FIGS, 4, 5 AND 6

Came in with a history of tuberculosis following influenza. Had positive sputum and had a recent severe hemoptysis. The first plates, no. 1889 (fig. 4), taken December, 1920, show an area lying close to the posterior wall in front of the seventh rib, mostly inside the midscapular line. This was thought to be a localized hydropneumothorax. That fluid was present was proved by aspiration, a needle being inserted in the seventh interspace, right back. A few days later, pneumothorax was begun and after the fourth treatment, plates No. 1964 (fig. 5) were taken. The changed position of the area described definitely disproves a localized hydropneumothorax and substantiates a diagnosis of cavity. In March, 1921, after the eighth treatment, the patient had a chill followed by a marked rise in temperature, and soon the characteristic signs of hydropneumothorax were heard. Fluid was removed from the pleural cavity in July, 1921, and replaced with air. This fluid re-formed, and it was decided to allow it to remain, in order to maintain the compression, meanwhile keeping close watch by physical examination and X-ray plates. A year after the first paracentesis, the aspirating needle was again introduced but no fluid was found. In March of this year, three years and three months after the first set of plates, plates no. 4286 (fig. 6) were taken. The lung has expanded and there is no evidence of cavitation. The trachea is drawn to the right as is the heart to a slight degree. The pleura is greatly thickened over the right side from apex to base. The right base is contracted. Clinically, the patient is doing very well.

FIG. 5. CASE 10. L. W. No. 1964. AFTER FOURTH PNEUMOTHORAX, SHOWING CAVITY DISLOCATED TOWARD SPINE. UPPER LOBE HELD OUT BY ADHESIONS

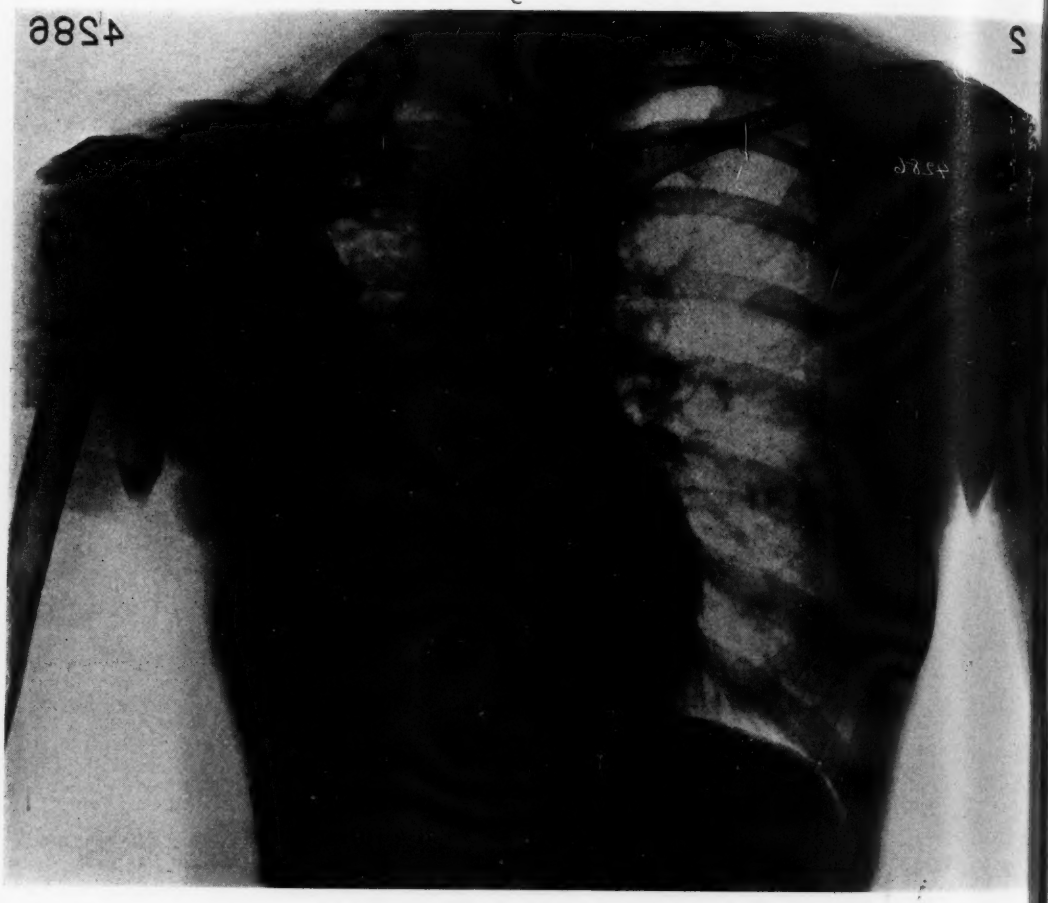

FIG. 6. CASE 10. L. W. NO. 4286. THREE YEARS AND THREE MONTHS AFTER PLATE 1889. LUNG EXPANDED; NO EVIDENCE OF CAVITY

INTRAPULMONARY CAVITATION IN TUBERCULOSIS

A CLINICAL, LABORATORY AND X-RAY STUDY OF 125 PATIENTS

B. J. WEIGEL[1]

The existence of cavitation in pulmonary tuberculosis is recognized as bearing a definite relation to its prognosis. According to Koch, eleven-twelfths of the deaths due to tuberculosis occur in patients suffering from pulmonary consumption, that is, that form of tuberculosis a chief characteristic of which is cavitation. The earlier a cavity is recognized and the better it is localized, the sooner definite measures directed toward its obliteration can be instituted, whether they be postural rest, artificial pneumothorax, or other means. This is especially true at present when pneumothorax is being employed more frequently and is begun earlier in the disease. When one recognizes the danger to which a cavity subjects the patient through its being the source of positive sputum which is poured out into the bronchial system and its affording the means for spreading the disease as pointed out by Gekler, *et al.* (*Journal American Medical Association*, February 9, 1924, vol. lxxxii), the importance of attacking any cavity early and persistently is realized.

There is no unanimity among the various observers and authors of textbooks on the physical signs characteristic of cavitation, such as the character of percussion note, changes in breath-sounds and types of râles. Some of the more common textbooks on physical diagnosis offer the following statements in reference to cavity diagnosis.

Osler enumerates cracked-pot resonance on percussion, cavernous or amphoric breath sounds, tubular breathing and sharp hissing breath sounds. Coarse bubbling râles which have a resonant quality on coughing may have a metallic ring or character. On coughing they are often loud and gurgling. In very large, thin-walled cavities, and, more rarely, in medium-sized cavities surrounded by recent consolidation, the râles have a distinctly amphoric echo simulating pneumothorax. The vocal resonance is greatly intensified and whispered bronchophony is heard.

[1] Albuquerque Sanatorium, Albuquerque, New Mexico.

The transmission of heart-sounds is also mentioned, as are Wintrich's and Gerhardt's phenomena.

Babcock states that "Inspection and palpation are of slight if any aid." He depends on percussion and auscultation. He mentions the tympanitic quality of surrounding dulness, as well as cracked-pot resonance, as presumptive evidence. Wintrich's, Gerhardt's, and Friedrich's phenomena are enumerated. Under auscultation, bronchial breathing and bronchophony, are mentioned Leube's *Nachklang*, that is, the whispered resonance or echo immediately following the loud word and seeming to be whispered; only, like a real echo it is not separated from the loud tone by an appreciable interval. Cavernous and amphoric breathing and voice are considered sufficiently characteristic under some circumstances if corroborated by other signs to diagnose cavitation. Metallic tinkle and metallic quality of breath sounds, voice, râles and percussion notes are enumerated as excellent proof.

Norris and Landis offer the most definite facts and figures on the subject. They point out that in large cavities (size of an orange) of the apex, percussion elicits a tympanitic note. They state that it is low-pitched and may have an amphoric or cracked-pot quality. The character of the breath-sounds, as heard over a cavity, are in the majority of instances cavernous or amphoric in quality and may be very loud and distinct or very distant, they state.

The spoken and whispered voice sounds are exaggerated. Whispered pectoriloquy, while not pathognomonic of cavitation, is the sign most constantly present. The metallic or amphoric cough is stressed. The presence of râles having a metallic quality is the most certain sign we possess. In a clinical and postmortem study of cavities, I found that in fifty cases there were seventy-six, of which fifty-eight were recognized during life. The eighteen escaping detection were for the most part small and centrally located.

Fifty-three out of fifty-eight (91.3 per cent): Whispered pectoriloquy was found.

Thirty-nine out of fifty-eight (67.4 per cent): Tympany (on percussion) was found.

Thirty-eight out of fifty-eight (65.5 per cent): Cavernous or amphoric breathing was found.

Thirty-three out of fifty-eight (58.6 per cent): Gurgling or consonating râles were found.

CASE NUMBER	X-RAY FINDINGS OF CAVITY	PHYSICAL EXAMINATION
1	L: apex to 2nd rib, 9 x 5 cm.	No cavity diagnosed
2	L: 1st interspace to 3rd rib, 5.5 x 3 cm. 3rd to 4th rib, 4 x 4 cm. R: 1st to 2nd rib, 2 x 3 cm. 1st rib to 2nd interspace, 4 x 3 cm. L. apex to 2nd interspace, 2 x 4 cm.	No cavity diagnosed
3	L: 2nd rib to 3rd interspace, 4 x 3 cm.	No cavity diagnosed
4	L: 2nd to 4th rib, 4 x 4 cm. Above and below, honeycombing	Cavity diagnosed
5	R: 1st to 2nd interspace, 4 x 2 cm.	No cavity diagnosed
6	R: beneath 2nd rib, 4 x 3 cm.	No cavity diagnosed
7	L: 1st to 2nd rib, 3 x 2½ cm.	No cavity diagnosed
8	L: beneath clavicle, 4 x 3 cm.	No cavity diagnosed
9	R: 3rd to 5th rib, 5 x 4 cm.	No cavity diagnosed
10	L: apex to 2nd interspace, 6 x 5 cm.	Cavity diagnosed
11	L: apex to 2nd rib, 7 x 4 cm.	No cavity diagnosed
12	L: apex to 2nd rib, 6 x 4 cm.	Cavity diagnosed
13	R: 1st rib to 3rd interspace, 5 x 3 cm.	No cavity diagnosed
14	R: clavicle to 2nd rib, 2 x 3 cm.	No cavity diagnosed
15	L: 1st to 3rd rib, 4 x 2 cm.	No cavity diagnosed
16	R: 3rd to 5th rib, 6 x 6 cm.	No cavity diagnosed
17	R: clavicle to 2nd rib, 4 x 3 cm.	No cavity diagnosed
18	R: 1st to 3rd rib, 7 x 3 cm.	No cavity diagnosed
19	L: clavicle to 4th rib, 7 x 5 cm.	No cavity diagnosed
20	L: apex to 5th rib, 17 x 6 cm. R: beneath clavicle, 4 x 3 cm.	Cavity diagnosed, 6th rib and 8th dorsal spine, upper left
21	L: 1st to 3rd rib	No cavity diagnosed
22	L: clavicle to 3rd rib, 6 x 4 cm.	No cavity diagnosed
23	L: beneath 2nd rib, 3 x 2 cm.	No cavity diagnosed
24	R: 2nd to 4th rib, 5 x 6 cm.	No cavity diagnosed
25	L: 2nd to 5th rib, 9 x 9 cm.	No cavity diagnosed
26	L: 1st to 3rd rib, 6 x 3 cm.	No cavity diagnosed
27	L: 1st to 2nd rib, 5 x 2 cm.	No cavity diagnosed
28	R: 2nd interspace, 3 x 3 cm.	No cavity diagnosed
29	L: clavicle to 2nd interspace, 8 x 5 cm.	No cavity diagnosed
30	R: behind clavicle, 2 x 3 cm.	No cavity diagnosed
31	R: apex to 2nd rib, 4 x 4 cm.	No cavity diagnosed
32	L: clavicle to 3rd rib, 4 x 3 cm.	No cavity diagnosed
33	L: 3rd to 4th rib, 3 x 4 cm.	No cavity diagnosed
34	L: clavicle to 3rd rib, 5 x 3 cm.	No cavity diagnosed
35	R: 2nd interspace, 2 x 2 cm.	No cavity diagnosed
36	L: apex to 3rd rib, 8 x 4 cm. R: 1st to 2nd rib, 3 x 2 cm.	No cavity diagnosed
37	L: 1st to 3rd rib, 7 x 5 cm.	No cavity diagnosed
38	L: 2nd to 4th rib, 4 x 4, 3rd to 4th rib, 3 x 2 cm. R: apex to 3rd rib, 5.5 x 4 cm.	No cavity diagnosed
39	L: 1st rib to 3rd rib, 6 x 4 cm. 3rd to 4th rib, 5 x 3 cm.	No cavity diagnosed
40	R: apex to 3rd rib, 6 x 6 cm. 4th to 7th rib, 7 x 7 cm.	No cavity diagnosed

CASE NUMBER	X-RAY FINDINGS OF CAVITY	PHYSICAL EXAMINATION
41	R: behind clavicle, 4 x 4 cm.	No cavity diagnosed
42	L: 2 small cavities, 2 cm. in diameter, 2nd interspace, and honeycombing	No cavity diagnosed
43	L: cavity 4½ x 3 cm., clavicle to 2nd rib	No cavity diagnosed
44	L: Honeycombing 2nd to 5th rib; one at 3rd rib, 3 cm. in diameter	No cavity diagnosed
45	L: cavity 2¼ x 2½ cm. back of 3rd rib	No cavity diagnosed
46	R: cavity 3 x 4 cm., 1st interspace and 2nd rib.	No cavity diagnosed
47	R: clavicle to lower 1st rib, 2 x 4 cm., 2nd interspace, 1½ x 1 cm. Honeycombing	No cavity diagnosed
48	L: honeycombed 1st to 3rd rib. Cavity 1 x 1 cm., back of 1st rib	No cavity diagnosed
49	L: clavicle to upper border 2nd rib, 5 x 4 cm. Cavity 2 x 2 cm. between 6th & 7th rib	No cavity diagnosed
50	R: cavity 1½ x 2 cm. back of clavicle. Cavity 1 x 2 cm. beneath 2nd rib	No cavity diagnosed
51	R: cavity 4 x 5 cm. between 1st & 2nd rib	No cavity diagnosed
52	L: cavity above clavicle to upper border 1st rib, 5 x 4 cm. Beneath 2nd rib, 2 x 2 cm.	No cavity diagnosed
53	L: cavity beneath 1st rib, 2½ x 2½ cm.	No cavity diagnosed
54	L: apex above 1st rib, 1 x 2 cm. 1st interspace, 2 x 1 cm.; 1st and 2nd interspace, 5 x 3 cm. R: 1st interspace, 2 x 4 cm. Honeycombing.	No cavity diagnosed
55	R: 1st interspace, 3 x 3 cm.	No cavity diagnosed
56	R: above clavicle, 2 x 2 cm. L: behind clavicle, 1 x 1½ cm. 1st interspace, 2 x 3 cm. Honeycombed 3rd interspace and behind 2nd rib, 3 x 3 cm.	No cavity diagnosed
57	R: 1st interspace, 5 x 3 cm.	No cavity diagnosed
58	L: behind 1st rib 3 x 1½ cm. to 1st interspace	No cavity diagnosed
59	L: supraclavicular, 4 x 2 cm. R: Behind 2nd rib, 1 x 1 cm. 4th interspace, 2 x 1 cm.	No cavity diagnosed
60	L: supraclavicular, 2 x 2 cm. R: below clavicle, 3 x 2 cm.	No cavity diagnosed
61	R: below clavicle to 1st rib, 4 x 4 cm.	No cavity diagnosed
62	R: lower clavicle to upper border 2nd rib, 4 x 3½ cm.	No cavity diagnosed
63	R: 1st interspace, 2 x 2½ cm.	No cavity diagnosed
64	R: Lower clavicle to upper border 2nd rib, 3 x 2½ cm. L: 3rd to 4th ribs, 1 x 1½ cm.	No cavity diagnosed
65	R: lower clavicular border to upper 2nd rib, 3½ x 2½ cm.	No cavity diagnosed
66	R: behind 1st rib, 2 x 1½ cm. 1st interspace, 2 x 2 cm. Behind 3rd rib, 3 x 2½ cm.	No cavity diagnosed
67	R: behind 2nd to 3rd rib, 3 x 6 cm. L: scattered ones; honeycombing.	No cavity diagnosed
68	R: behind clavicle, 3 x 4 cm. Horseshoe-shaped, 4 cm. wide, 1st interspace. L: behind 2nd rib, 1 x 1, honeycombing both sides	No cavity diagnosed

CASE NUMBER	X-RAY FINDINGS OF CAVITY	PHYSICAL EXAMINATION
69	L: above clavicle, 2 x 2 cm. False cavity.	No cavity diagnosed
70	L: below clavicle 3 x 3 cm., 2nd interspace, 2 x 2 cm. R: above clavicle 1 x 1, behind 1st rib, 3 x 2½, 8th interspace 2 x 2 cm.	Cavity 1st rib to 2nd interspace diagnosed
71	L: beneath 1st rib, 2 x 2 cm. R: lower border 1st rib to 2nd interspace, 5½ x 3½ cm.	No cavity diagnosed
72	L: 1st interspace, 3 x 2 cm.	No cavity diagnosed
73	R: Upper border of clavicle to 2nd rib, 7 x 6 cm.	Cavity diagnosed beneath clavicle
74	R: upper border of clavicle to upper border 2nd rib, 7 x 3½ cm.	No cavity diagnosed
75	L: 2nd interspace 2½ x 2½ cm.	Cavity diagnosed, 4th rib to 2nd rib
76	R: behind 1st rib and 1st interspace 4 x 5 cm. L: 1st interspace 3 x 3, and one above this, 2 x 2 cm.	No cavity diagnosed
77	R: behind 1st rib, 2 x 2½ cm.	Cavity diagnosed, clavicle to 2nd rib
78	L: 2nd interspace, 2 x 2½ cm.	No cavity diagnosed
79	R: above 1st rib to upper border 2nd rib, 7 x 2½ cm.	No cavity diagnosed
80	R: apex to lower 2nd rib, 10 x 4½ cm.	No cavity diagnosed
81	L: above clavicle to upper border 2nd rib, 6 x 6 cm. Honeycombing	Cavity suspected
82	R: 1st interspace, 2½ x 2½ cm.	Cavity diagnosed, clavicle to 2nd rib
83	L: behind 1st rib, 2 x 3 cm.	No cavity diagnosed
84	L: 1st interspace, 2 x 1½ cm., 2nd interspace, 2 x 2 cm.	No cavity diagnosed
85	L: between clavicle and 2nd rib, 3½ x 3½ cm.	No cavity diagnosed
86	R: upper border of clavicle to lower border 1st rib, 6 x 4 cm.	No cavity diagnosed
87	L: behind 2nd rib, 1½ x 1½ cm.	No cavity diagnosed
88	L: 2nd interspace, 4 x 4 cm. R: behind 1st rib, 3 x 2½ cm.	No cavity diagnosed
89	L: 1st interspace, 3 x 4½ cm. Honeycombing below	No cavity diagnosed
90	R: clavicle to 2nd rib, 6 x 4 cm., 2nd interspace, 2 x 1½ cm.	Cavity diagnosed, clavicle to 2nd rib
91	L: apex, 10 x 6 cm.	Cavity diagnosed, 1st to 3rd rib
92	R: apex to 2nd rib, 8 x 5 cm.	Cavity diagnosed, apex to 2nd rib
93	R: 1st interspace, 3 x 3 cm.	Cavity diagnosed, 2nd to 3rd rib
94	R: behind 1st rib, 3 x 3 cm.	No cavity diagnosed
95	R: behind 1st rib, 3½ x 3 cm.	No cavity diagnosed
96	R: upper border of 1st to upper border of 2nd rib, 4½ x 5 cm.	Cavity diagnosed, right apex to clavicle
97	L: behind 2nd rib, 1½ x 1 cm. R: apex to 2nd rib, 9 x 7 cm.	Cavity diagnosed, right apex to 2nd rib

CASE NUMBER	X-RAY FINDINGS OF CAVITY	PHYSICAL EXAMINATION
98	R: above clavicle to 1st rib, 4 x 4 cm. 1st interspace, 3 x 4 cm.	Cavity diagnosed, 1st to 2nd rib
99	R: 1st to 3rd rib, 8 x 4 cm.	Cavity diagnosed
100	R: above 1st rib, 1 x 1 cm. L: apex to 3rd rib, 9½ x 7 cm.	No cavity diagnosed
101	L: 1st to 3rd rib, 9½ x 7 cm.	No cavity diagnosed
102	L: apex to 3rd rib, 11 x 9 cm.	Cavity diagnosed, apex to 1st interspace
103	R: behind 1st rib, 1½ x 2 cm. L: apex to 2nd rib, 7 x 4 cm.	No cavity diagnosed
104	R: apex to 3rd rib, 8½ x 7 cm. L: 2nd to 4th rib, 6 x 4 cm.	No cavity diagnosed
105	R: above clavicle, 2 x 2 cm.	No cavity diagnosed
106	L: lower 1st to lower 2nd rib, 4 x 3 cm.	No cavity diagnosed
107	R: apex to 2nd rib, 6 x 5 cm. Honeycombed to 5th rib L: behind 1st rib, 1½ x 1½ cm. 1st interspace 2 x 2 cm. Honeycombed below	Cavity diagnosed, apex to 1st rib, right side
108	R: above clavicle to 2nd rib, 7 x 4 cm.	Cavity diagnosed, 1st to 3rd rib.
109	R: 1st interspace, 3½ x 3½ cm.	No cavity diagnosed
110	R: 1st interspace, 1 x 3 cm. L: 1st to 3rd rib, 7 x 3½ cm.	No cavity diagnosed
111	R: clavicle to 3rd rib, small communicating cavity	Cavity diagnosed, clavicle to 1st rib
112	L: 1st interspace, 4 x 5 cm. R: clavicle to 2nd rib, 4 x 4 cm.	No cavity diagnosed
113	L: 1st interspace, 2 x 3 cm.; 3rd interspace, 1½ x 1½ cm.; 3rd interspace, 2 x 2 cm. R: 1st interspace, 3 x 3 cm.	No cavity diagnosed Suspicious right upper
114	R: behind 3rd rib, 1½ x 1½ cm.	No cavity diagnosed
115	L: behind clavicle, 3 x 3 cm.	No cavity diagnosed
116	L: above 2nd rib, 4 x 4 cm.	No cavity diagnosed
117	R: apex to lower 1st rib, 4 x 3 cm.	Small cavity diagnosed under 1st rib
118	R: apex to 5th rib, 17 x 12 cm. L: 1st to 3rd rib, 4 x 5 cm.	Cavity diagnosed, clavicle to 1st rib, right
119	R: upper border of 1st to lower border of 2nd rib, 5½ x 5½ cm. L: upper border of clavicle to lower border of 2nd rib, 6½ x 7 cm.	Cavity diagnosed, both uppers
120	L: 1st to 3rd rib, 4 x 2 cm.	No cavity diagnosed
121	R: 1st interspace, 3 x 4 cm.	No cavity diagnosed
122	L: apex to 2nd interspace, 10 x 8 cm.	No cavity diagnosed
123	R: apex to 2nd rib, 7 x 6 cm.	Cavity diagnosed, 2nd to 3rd rib
124	L: 3rd rib to apex	No cavity diagnosed
125	L: 3rd rib to clavicle	No cavity diagnosed

Butler very conservatively states that the presence of a cavity cannot always be determined with certainty. He enumerates tympanitic, dull tympanitic, amphoric or a cracked-pot percussion note, Wintrich's and Gerhardt's phenomena, bronchial, cavernous or amphoric respiration, whispered pectoriloquy, or amphoric bronchophony, and large gurgling or bubbling râles which may have a ringing metallic or amphoric quality.

The accompanying tabulation of the findings in 125 cases was made from the material at the Albuquerque Sanatorium, to determine from a practical standpoint the frequency with which physical signs corroborated X-ray and other findings. These were all cases that presented fair-sized cavities, that is, 2 x 2 cm. or larger. Cavities 1 x 1 cm. occurring in this tabulation were either communicating with larger ones or part of honey-combing. The 125 cases presented 175 distinct cavities. All the cases in this series except case 69 either had positive sputum over a long period under our observation or gave a history of positive sputum on repeated examinations.

As to location, cavitation was exclusively right-sided in 49, or 39.5 per cent of the cases; left-sided in 51, or 41.1 per cent; bilateral in 24, or 19 per cent. One hundred twenty-one, or 69.5 per cent, of the cavities were located above and within the second interspace; 38, or 21.5 per cent, were located within and below the second interspace; 16, or 9 per cent, were located below the second interspace. Twenty-six cavities, or 15.4 per cent, were limited to the apex. On clinical examination, diagnosis of cavity was made in 25, or 20 per cent, of the patients. In one case cavity was suspected. Twenty-six cavities were diagnosed (bilateral cavitation in one case), or 14.8 per cent. Honeycombing, or small communicating cavities, were present in 13 cases, or 10.4 per cent.

Cases showing annular, or ring shadows, were present in this series. The work of Lawrason Brown *et al.* (AMERICAN REVIEW OF TUBERCULOSIS, 1919, ii, 664), as well as the work of A. K. Stone and others, calls one's attention to the fact that not all ring shadows appearing on the X-ray film mean cavitation. It is true that scar tissue, a thick-walled upper-lobe bronchus, and the margin of a rib, may combine to form a circular shadow that is confusing. Ring-shaped pleural shadows are also occasionally encountered, and must be differentiated from intrapulmonary changes. However, from our experience, it is thought that localized pneumothoraces and interlobar pleurisies or empyemas do

not occur as frequently as one is led to believe by Brown and others. It is noteworthy that the pathologists have not reported finding localized pneumothoraces, particularly interlobar ones, as well as interlobar exudates and empyemas, with the same frequency that one would be led to expect them from Brown's work. He mentions in support of his thesis that a number of these annular shadows disappeared during the progress of treatment in from six to eight months. It is not impossible for genuine pulmonary cavity to disappear in that length of time without any special measures being taken to secure that end. We have seen this happen and have felt that disappearance of sputum, which accompanied the disappearance of the X-ray shadows which we had interpreted as cavities, was further corroboration of the actual obliteration of the cavity. The differential diagnosis between a ring shadow and intrapulmonary cavitation rests on correlation between history, physical signs, laboratory findings, and X-ray interpretation. It is certain that a case having persistently positive sputum and showing a ring shadow must, after excluding bronchiectasis, be accepted as having a tuberculous cavity. One case in the series here presented (case 69) shows a ring shadow, 2 x 2 cm., on the left side above the clavicle. This was diagnosed as a false cavity on the absence of physical signs in this area and the absence of positive sputum. At our institution we have several times seen instances in which patients presenting ring shadows on X-ray films had been assured that the shadow was the remnant of an interlobar exudate or a localized pneumothorax, when careful fluoroscopic examination revealed fluid in these areas. When, in addition, it is possible to drain this fluid by having the patient lie on the other side, the diagnosis of a pleural ring or interlobar exudate was made still more uncertain. This with the persistently positive sputum made cavitation certain.

It might be of interest to note that 37 of these 125 patients, or 29.6 per cent, are known to be dead. Twelve cases have passed from our observation and it is doubtful whether they are living. Forty patients, or 32 per cent, had pneumothorax over a long enough time, so that obliteration or shrinking of their cavities was noted with a decrease in the amount of expectoration. In three of the patients, the cavities were opened (Gekler, *et al.*, *Journal American Medical Association*, February 9, 1924, lxxxii, 457) for chemical sterilization.

Various authors give prominence to different signs encountered in pulmonary cavitation. Ordinarily none agree on any definite findings.

Norris and Landis offer the only figures in the more common textbooks on chest diseases. The cases presented in their tabulation were necessarily, for the most part, moribund; otherwise, it does not so happen that one has the opportunity to make post-mortem studies. This probably accounts for the fact that whispered pectoriloquy was found by them as the most frequent sign. The cases in our series were all of them patients able to make the trip from their homes to Albuquerque in search of their health and, with rare exceptions, could not in any sense of the word be called moribund. They were not emaciated to the degree one finds in terminal cases so frequently in hospitals for incurable consumptives in our large cities. Inspection, mensuration, palpation and percussion may be disregarded, as far as their practical value in cavity diagnosis is concerned. The only signs of any value appear to be those elicited on auscultation. Roughly, they may be classified into breath and voice-sounds and râles. Breath-sounds modified to a blowing or tubular quality must arouse suspicion, but are just as apt to indicate consolidation or fibrosis, and are therefore not conclusive. Post-tussal suction, when encountered, is almost invariably indicative of cavitation. Whispered pectoriloquy, for ordinary purposes, is considered very uncertain. The thickness of the chest wall has to be taken into consideration, as well as the location of the area, etc. In quite a number of cases a trachea pulled to one side and scar tissue extending toward the periphery produces this phenomenon over a rather large area. Areas of consolidation, when located near the surface, will also produce pectoriloquy. Metallic râles may be present and, when found, have in our experience always been indicative of the presence of a cavity. These râles have the same metallic tinkle as one hears over the collapsed side in a large pneumothorax on cough, except that the metallic feature is not so clear and bell-like. Gurgling râles, especially when heard between the third rib and clavicle on the left side, arouse our suspicion and in most instances indicate cavitation in this area. The value of such signs as Wintrich's, Gerhardt's and Friedrich's phenomena, as well as Leube's *Nachklang*, is certainly very doubtful. The cases presenting these phenomena are interesting for teaching purposes, but are so exceptional that it is hardly worth the while of the examiner to look for them as a routine procedure. The question confronting the physician is this: Does the patient, or does he not, have pulmonary cavitation? The shortest and easiest means of arriving at the correct answer is the one that should be employed. Given history of sputum in sufficient quantity that is persistently posi-

tive for tubercle bacilli, and a rarefied area on the X-ray film, diagnosis of cavity should be accepted regardless of the physical signs. We feel that the interpretation of X-ray plates of the chest should be made, not by the roentgenologist, but by the clinician who has elicited the physical findings. It is the correlation between the physical findings and the X-ray findings that establishes the diagnosis of any chest condition and not one set of findings alone. We feel further that there are all too many men interpreting chest X-ray plates who lack extensive clinical and pathological experience. When a doubtful ring shadow presents itself on the X-ray film, we would place the burden of proof on the side disputing the existence of true cavitation. We believe that it is much safer to treat the patient having these findings as a cavity case than to speculate about the probability of an artifact. The use of the fluoroscope must again be emphasized and, if the rarefied area can be detected under the screen and, on moving the patient, a fluctuating fluid level is discerned, one is positive of cavitation. In our experience, it is the exception rather than the rule for definite cavity signs to be present except in far advanced practically moribund cases. Since the diagnosis of cavity must be made early in order to achieve any success with treatment, it is a mistake to wait until physical signs demonstrate the cavity before accepting a diagnosis and instituting treatment.

SUMMARY

1. Physical signs in intrapulmonary cavitation are very uncertain. Writers appear to be at sea as to the relative value of different signs.

2. Out of 175 cavities, 26, or 14.8 per cent, were diagnosed on physical examination.

3. History, clinical and laboratory findings, when correlated with the X-ray, constitute the only means of definitely diagnosing cavitation. Persistently positive sputum in the absence of bronchiectasis must, as a rule, be accepted as indicative of destruction of lung tissue.

4. These findings, when accompanied by areas of rarefaction on the X-ray film, determine cavitation.

5. The best signs on clinical examination are breath and voice-sounds of a metallic character, as well as râles that possess metallic tinkling. Soppy, gurgling râles are also common findings.

6. Neither the clinician, on his findings alone, nor the roentgenologist, on his findings, can be positive that cavitation exists. There must be correlation between history, physical findings, laboratory and X-ray before definite conclusions are justified.

CHOLESTEROL ESTERS OF THE BLOOD IN TUBERCULOSIS[1,2]

H. C. SWEANY

In a study of the chemistry of the blood in tuberculosis, Sweany, Weathers and McCluskey (1) observed various deviations from the normal and described some of them. The most noteworthy of these changes was in the lipoids. These ingredients increase in the proliferative types of tuberculosis and decrease in the exudative types. While no valid cause of these changes was found it was suggested that the cholesterol increase may be actuated by the healing forces of the body to act as a "tampon," and thus to absorb or neutralize toxins produced either directly or indirectly by the tubercle bacillus. It is common knowledge that cholesterol protects red blood corpuscles from hemolysis against various toxins such as cobra venom. It may, therefore, protect not only red blood cells but all body cells against other toxins. It will also check the hemolytic action of lecithin, which rises in favorable types of tuberculosis but which does not rise to the same level as the cholesterol compounds. This change in lecithin has been demonstrated by McCluskey (2) in a more recent and yet unpublished work in which the various phosphorus compounds were studied. The lecithin phosphorus was found to increase and the acid-soluble phosphorus decrease in the proliferative types of tuberculosis, while the reverse was true in the exudative types. Five groups were chosen to represent the more common types of the disease as a matter of convenience only. Group I represents patients with massive involvement who are failing; group II, those with the same involvement who are holding their own—a neutral group, group III, the same, only with moderate involvement; group IV, patients with moderate involvement, but improving and with definite proliferation; and group V, the same as IV but with massive involvement.

[1] From the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May, 1924.

EXPERIMENTAL

In the present work a special study has been made of cholesterol and its esters and the partition of these between the cells and plasma. Only representatives of the extreme groups have been included in this rather small series. This is for the purpose of showing in a simple manner the most important results of a series of about 25 cases that will be reported later in more detail. All analyses were carried out as previously described, with two exceptions. First, analyses were done on plasma and whole blood of the same specimen. From these data and from the cell-plasma ratio, the partition of cholesterol and its esters between cells and plasma was determined, and the concentrations in cells and plasma and various ratios were calculated. Second, the cholesterol-digitonide

TABLE 1

Showing partition of cholesterol and its esters of the blood between cells and plasma in the extreme types of tuberculosis

	PATIENT					
	A.O.	H.T.	H.H.	R.Mo.	R.Mi.	T.H.
	Group I (after death)	Group I	Group IV	Group IV	Group V	Group V
Per cent cells	30.5	31.	44.2	43.4	39.	41.5
Total C in whole blood	114.9	127.	208.	188.6	347.2	272.
Total C in cells	63.3	64.	78.5	81.2	93.4	116.9*
Total C in plasma	51.6	63.	129.5	107.4	253.8	175.1
Free C in plasma	29.	36.2	45.8	32.8	142.	3.
Esters in plasma	22.6	26.8	83.7	74.6	110.6	176.6

*24 mgm. of esters, the only one so found, may have been an error.

was precipitated out with an alcoholic extract of digitalin instead of pure digitonin. It was found that this method was just as good and far less time-consuming than the modified Windaus method described by Bloor (3). I am grateful to my colleague, Dr. K. Lucille McCluskey, for this simplification in technique.

The results are shown in table 1.

It is quite evident from these figures that the esters are the most variable of all the blood lipoids, and that the esters are, with one questionable exception, confined solely to the plasma. This simplifies matters considerably, because it renders analysis easier and shows a greater contrast between the progressing and failing patients.

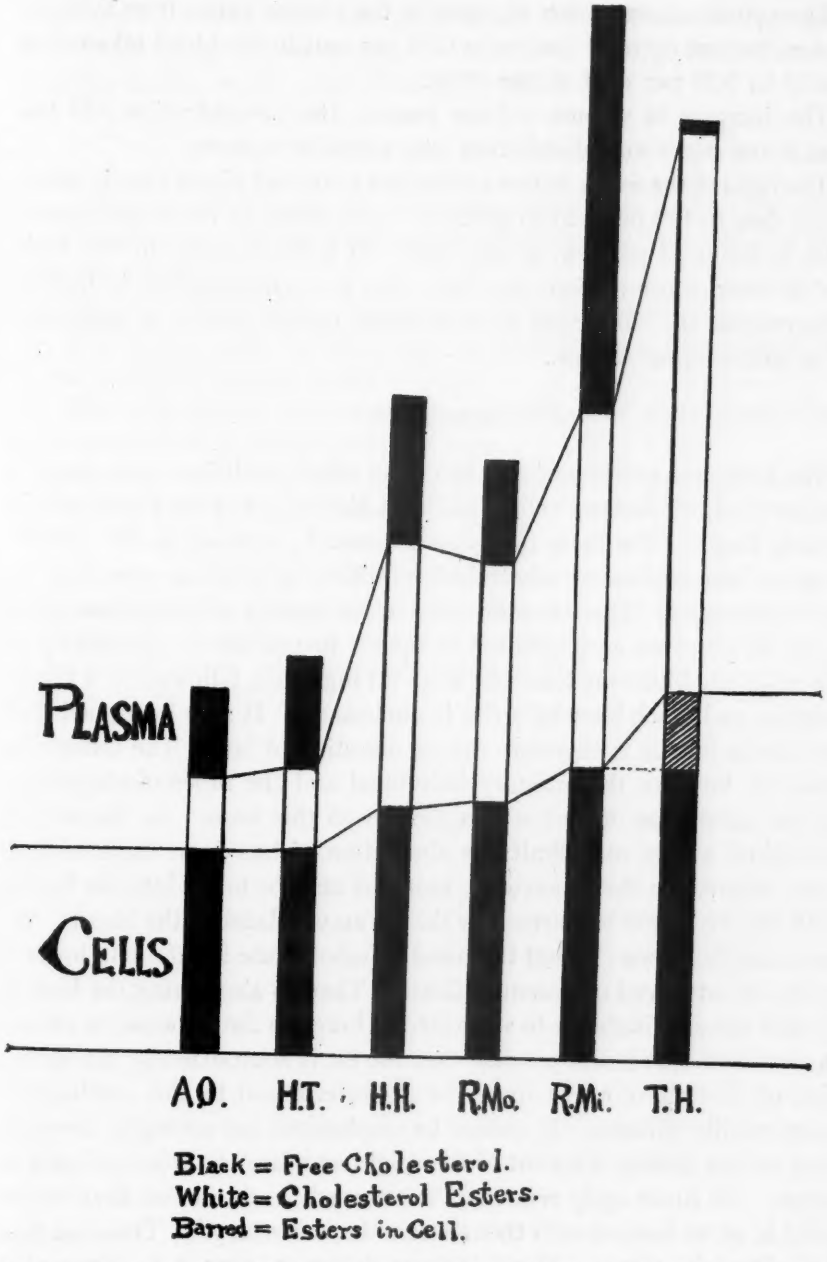

CHART 1. SHOWING THE PARTITION OF CHOLESTEROL AND ITS ESTERS IN THE BLOOD OF TUBERCULOUS PATIENTS

The actual concentration of esters in the plasma varies from 0.06 per cent at the one extreme (as low as 0.04 per cent in the blood taken after death) to 0.25 per cent at the other.

The increase in plasma volume renders the concentration still less than if the esters were distributed over a smaller volume.

The ratio of the esters to free cholesterol is around 33 per cent in group I and rises to 120 per cent in group V. According to Bloor this normal ratio is about 33 per cent of the total. It is the increase in this ratio and in ester concentration, therefore, that is so characteristic in healing tuberculosis, and the actual decrease below normal that is an indication of an unfavorable outlook.

DISCUSSION

We have not overlooked the fact that other conditions may cause a similar rise in cholesterol values, and that diet may alter the values within certain limits. The facts that were presented pertained to the various stages of uncomplicated tuberculosis in which the patients were kept on an average diet. There is something in the healing of tuberculosis that seems to cause an accumulation of lipoids in the blood. According to Bloor (4) the blood-fat rises first after fat ingestion, followed by a rise in lecithin, and much later by a rise in cholesterol. It may be argued that the rise in lipoids is therefore due to ingestion of fats. The difference, however, between the ordinary individual and the tuberculosis patient on the same type of diet is inexplicable on this basis. In the normal individual nature may limit the absorption of fats from the intestinal tract, whereas in the tuberculous more fat may be taken into the lymph than can be stored or burned, so that it accumulates in the blood. We have clearly shown (1) that the basal metabolic rate is definitely lowered in the far advanced quiescent patients. There is also during the healing of such cases an inability to store fat. Therefore the fat must be carried in the blood. It is also possible that the fat is neutralized by the formation of cholesterol esters from the cholesterol and in this condition is more readily utilized. It cannot be emphasized too strongly, however, that we are utterly ignorant of the origin and fate of cholesterol and its esters. As Bloor aptly remarks, "After much work, we feel that cholesterol is, as we have always thought it to be, a mystery." The same may be said of its esters. These findings, however, cannot be diregarded. There surely must be functions other than the ones already known.

There must be some cause and purpose for these substances that exist in twice the concentration of sugar of the blood. A large field of work is therefore opened up for research in lipoid metabolism.

SUMMARY

1. The total cholesterol of the plasma decreases below the total cholesterol of the cells in exudative tuberculosis and vice versa in proliferative tuberculosis.

2. There is little, if any, cholesterol ester in the corpuscles.

3. Cholesterol esters in the plasma increase to about three times the normal values in healing fibroid phthisis.

4. The ester-free cholesterol ratio also increases to about three times the normal value in the proliferative type.

5. The ester concentration decreases to nearly half the usual value in unfavorable and terminal cases.

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HEMOPTYSIS IN ASSOCIATION WITH EPIDEMIC COLDS IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Hemoptysis in pulmonary tuberculosis cases, when produced by acute congestion, in other words, a cold, was described by Laennec and various later writers. Early in the present century the Phipps Institute Staff (1) called attention to the fact that blood-spitting due to this cause was observed in epidemics, and was probably due to the pneumococcus. In an article in 1911 (2) I described such an epidemic at the White Haven Sanatorium, while Montgomery (3) reported another at the Chestnut Hill Home for Consumptives.

Beginning about January 1, 1923, and ending some time in April, 1923, an epidemic of colds, in which Philadelphia participated, prevailed throughout the country. During its existence a much larger percentage of my patients spat blood than usually. The following is a report on all my tuberculosis patients who manifested a cold with or without blood-spitting, and who had blood-spitting with or without a cold during this period. The first blood-spitting associated with a cold occurred on January 1 and the last April 7.

Among my adult tuberculosis patients 46 had their colds in the form of acute bronchitis, and of these 46, 17 (36.9 per cent) spat blood during the activity of the bronchitis. Eight others spat blood several weeks after the bronchitis, apparently in association with an exacerbation of the tuberculosis. The cases divide themselves as follows:

Acute bronchitis with blood-spitting	17
Acute bronchitis without blood-spitting	20
Acute bronchitis without blood-spitting, followed by exacerbation of the tuberculosis with blood-spitting	8
Acute bronchitis without blood-spitting, followed by exacerbation of the tuberculosis without blood-spitting	1

In addition to these, and not classified with them, there were 5 patients who had a cold in the form of acute coryza, 4 with blood in the nasal discharges and one without. Though they had typical epidemic

colds, they were not classified with the preceding because bronchitis or acute congestion of the lower respiratory tract was lacking, without which blood-spitting could not be expected. They are reported because I am inclined to think that the blood in the nasal discharge of these cases is due to oozing from a congested nasal mucous membrane, as is the case with blood expectorated in the bronchitic cases from a congested bronchial mucous membrane.

To make the record of all the patients who spat blood during these fourteen weeks more complete I report 12 more who spat blood without distinct evidences of a cold, 5 apparently due to breaking down and 7 due to unknown causes.

In my clinical and pathological experience the two common causes of hemoptysis in pulmonary tuberculosis appear to be (1) acute congestion in the way of a bronchitis or pneumonia and (2) the opening of a tubercle or tuberculous mass into a bronchial tube with the expectoration of caseous matter and blood, or the temporary healing of a small or large cavity with a similar result on its reopening.

1: In acute congestion: In the case of congestion, the hemoptysis is usually small, and in the form of blood-streaked or bloody sputum, or a mouthful of blood. It is usually among the first of the symptoms. It appears to be due to oozing from the area of congestion, and to be similar to what occurs in the case of a cold in the head when we find blood, as well as pus, in the nasal discharge. Though usually small in amount, I have seen the hemoptysis as large as eight ounces for three or four days in cases of lobar pneumonia associated with tuberculosis; and though usually not frequently repeated I have seen it both at the time of onset and at the time of the subsidence of the congestion, and sometimes continue throughout the duration of the cold.

I have, for instance, four or five cases similar to the following:

Male, aged 36. Active incipient tuberculosis in 1904 with arrest of the disease after six months in White Haven Sanatorium. Attack of appendicitis in February, 1906, with relapse of tuberculosis of the lungs and return to sanatorium, where the disease was again arrested, and he remained well till December 23, 1915, when he had an acute left lower lobar pneumonia with a temperature of 103° for nine days and ending by crisis. During this whole time he spat blood freely, one-half to one ounce for five or six days, when it gradually lessened. The pneumonic consolidation cleared up entirely, and he has been well ever since.

The important symptoms in the diagnosis of the common broncho-pulmonary cold are elevation of temperature, increase in cough and expectoration, onset of pain or soreness, especially substernal soreness not

previously experienced, and an accompanying or preceding cold in the head or tonsillitis. Another important diagnostic feature is the presence of other colds in the ward or household, especially associated with blood-spitting. Blood-spitting of this character is sometimes seen in patients who have already accomplished a practical cure, and in my experience has no untoward significance.

2. *Ulceration of tubercle:* When a tubercle or tuberculous mass breaks into a bronchial tube it is somewhat similar to a boil or abscess opening on the surface of the body. When it breaks, if the split is at all into healthy tissue, bleeding ensues. And I have no doubt but that every progressive case with tubercle bacilli in the sputum, associated as it must be with breaking down of tubercles, bleeds more or less, from a mere speck of blood to any larger amount, with the breaking down of the majority of these tubercles. Depending on where, in the bronchopulmonary passages, the tubercle breaks and the length of time before the caseous material is expectorated, the blood may appear in the sputum, or be absorbed, or be so distributed through the sputum as to be unnoticeable. It is probable that some individuals absorb the blood more readily than others.

This variety is usually preceded by an elevation of temperature, more or less marked symptoms of toxemia, a sensation of constriction or tightness in the chest and, sometimes, more cough. Then, with a sudden increase of expectoration of caseous matter there comes more or less blood, from a few drops to a mouthful, or rarely more. As a rule, when the excitement of the blood-spitting has subsided, the patient feels better, the temperature declines, the cough eases, and the feeling of constriction disappears. For instance,

Male, aged 30. Far advanced case, improving, but not yet quiescent. Temperature for several weeks 99.6°. Had rise of temperature to 101° and soreness across chest for two days when he, according to his statement, "expectorated what looked like the core of a boil associated with bloody sputum and immediately after he felt better," and the temperature that evening was down to its usual mark.

In the case of a cold the hemoptysis usually occurs at the beginning of the new, or the increase of the old symptoms, while in the case of breaking down of a tubercle, it usually occurs after the new symptoms have been in progress some time. After hemoptysis from a cold the symptoms usually continue, or may even increase in severity for some time. After hemoptysis from breaking down the symptoms improve almost at once, and the patient feels better. An hemoptysis from break-

ing down oftentimes occurs three to eight weeks after a process capable of producing renewed activity, like a severe cold, or other acute disease, after a confinement, or a protracted period of over-work. It is not uncommon, therefore, to have an hemoptysis from a cold, and three to eight weeks later another hemoptysis from a relapse of the tuberculosis, due to the activity produced by the cold.

In this series, blood-spitting was the first symptom of the cold in five cases; it occurred within twenty-four hours after other symptoms, like cough, expectoration and fever in three cases; it occurred on the second day in three cases, on the fourth day in two cases, on the sixth day in one case, on the ninth in one case, and with a relapse of the cold on the 28th day after its original beginning in one case. The exact day was not evident in one case, though it was within the first three or four. The amount of blood was blood-streaks over one day, seven cases; blood-streaks over two days, one case; one-half ounce over two days, one case; one ounce over eight days, one case; four ounces over two days, one case; five and a half ounces over three days, one case; twelve ounces over two days, one case; large clots over one day, one case; large clots over five days, one case; and large clots over nine days, one case.

In this series blood-spitting associated with renewed activity or exacerbation of the tuberculosis occurred between 22 and 107 days after the beginning of the cold. The amount of blood expectorated was blood-streaked sputum over one day, one case; over two consecutive days, one case; over four consecutive days, one case; one ounce over four consecutive days, one case; bloody sputum over three consecutive days, one case; bloody sputum over two nonconsecutive days, one case; two ounces in one day and five ounces in another, one case; four ounces in one day and four ounces in another, one case.

Following are all the cases, occurring in my practice, that had a cold or blood-spitting from January 1, 1923, to April 7, 1923:

Case Reports

1. Seventeen cases with the cold in the form of acute bronchitis with blood-spitting or frank hemoptysis apparently due to the cold

Case 1: Male, aged 23. Early case in condition of arrest. Blood-streaked sputum January 1, 1923, with increase in cough and expectoration lasting one week. Manifested slight evidences of exacerbation of the tuberculosis from January 30 to February 12 without blood-spitting. He spat blood four other times since June, 1922.

Case 2: Male, aged 53. Far advanced case, improving rapidly. The cough and expectoration had completely subsided when he developed a cold on January 3, 1923, with bloody spu-

tum and a return of the cough and expectoration. The cold was entirely well in a week. The only other time he spat blood was in June, 1922.

Case 3: Male, aged 68. Very old fibrous case with chronic endocarditis. Condition of apparent cure for many years. Developed cold on January 3, 1923, with considerable cough and expectoration, and blood-streaked sputum. Well in about three weeks. Spat blood only once before, namely, in 1899.

Case 4: Female, aged 23. Very far advanced, slowly progressing case, in bed practically continuously for past two years. She had considerable cough and expectoration, and always slight elevation of temperature. Without noticeable increase in any of these symptoms she spat blood in the form of large clots almost daily between January 8 and January 17, 1923, while another member of the family was suffering from the typical epidemic cold. She had not been accustomed to spitting blood. During the last four years, while under my care, she spat blood in the midst of a cold in August, 1919, when she spat blood clots, and also in November, 1919, when she spat blood-streaked sputum.

Case 5: Female, aged 52. Extremely far advanced case, living over the past five years only by extraordinary care on the part of a devoted husband. She was never up more than several hours, and then only to sit by a window. Her cold began January 8, 1923, with a dry, harassing cough, which became productive about January 12, when she had a day of blood-streaked sputum. The respiratory symptoms continued about two weeks, and just as they were gone she developed gastrointestinal symptoms, with pain in the epigastric region, and a rising temperature to 101°. It appeared like a relapse of the cold in the form of gastroenteritis. The abdominal disturbance was associated with gas, and produced great shortness of breath. She died February 21, 1923. Death was apparently caused by this cold, though she was so ill that it required very little to cause death. During the past five years she spat blood in small quantities over several days seven or eight times, but almost always in association with a definite cold or several weeks after a cold, when slight exacerbation might be expected.

Case 6: Male, aged 26. Moderately advanced case, improving rapidly. Cough and expectoration very slight. With slight increase in cough, but without elevation of temperature or pulse-rate, he spat blood-streaked sputum on January 15, 1923, and January 17, six drams of blood on January 18, and blood-streaked sputum on the 19th, 20th, 22nd, 24th and 25th. He spat blood twice before in the last three years; one of these times was as follows: On April 3, 1922, temperature rose to 100°, and for the next five days it was 100.4° to 100.8°. It became normal again on April 13. On April 7 he spat streaked sputum. On April 10 he had a hemoptysis of 1 1/2 oz. at 1 P.M., again at 3.30 P.M., and April 11 streaked sputum. No blood-spitting thereafter. The cause of the blood-spitting both times appeared to be an acute cold.

Case 7: Male, aged 25. Extremely far advanced case gradually improving, though still absolutely confined to bed. Cold began January 28, 1923, with increase in cough and expectoration. On January 30 the sputum was blood-tinged. Examination showed increase in râles over left side. There was no rise in temperature. The cough and expectoration and interference with breathing increased until he died on February 12, 1923, death apparently being precipitated by the cold. Spat blood seven or eight times during the four years before death.

Case 8: Female, aged 36. Far advanced case, improving slightly. She developed a cold lasting eight days, with pain in the chest and a temperature of 101°, and increase in cough and expectoration. She spat blood-streaked sputum over one day (1/28/23). She never had pain or blood-spitting before.

Case 9: Male, aged 30. Moderately advanced, arrested case doing light work. Cough and expectoration at a minimum. On February 3 at 8 P.M., without warning, an hemoptysis of one dram; February 4 at 8 A.M., hemoptysis of two drams, and at 11 P.M., hemoptysis of

three ounces; February 5 at 5 A.M., hemoptysis of two ounces. Cough and expectoration increased, but subsided again in about a week. No elevation of temperature. The râles in the chest also increased, with a return to the previous condition in about two weeks. He spat blood before in the spring of 1919 and in August, 1922.

Case 10: Male, aged 26. Early case in condition of arrest, with practically no cough or expectoration. Working. Cold began on February 14, 1923, with principal symptom increase in expectoration; and on February 15 he woke up at 2 A.M. with a mouthful of blood, and another mouthful followed immediately. He thought the whole amounted to about three drams. There were a few streaks all that day. The cold lasted only several days. He spat blood twice before: In February, 1920, hemoptysis of six ounces in association with pleurisy; February 22, 1921, hemoptysis of eight ounces in association with a typical cold.

Case 11: Female, aged 41. Far advanced case doing extremely well. On forty minutes' exercise and three hours' cure. Just increased twenty-five pounds in weight. Her cold, manifested by increased cough and expectoration, lasted from February 19, 1923, to March 1, 1923. She spat blood-streaked sputum on February 28, 1923. The temperature remained normal. She spat blood previously in 1919, 1920, and 1921.

Case 12: Female, aged 22. Far advanced case, improving rapidly, with no cough or expectoration. She developed a cold on February 22, 1923, with cough, expectoration and elevation of temperature to 101°, where it remained with slight remissions till March 8, when she developed acute lobar pneumonia of right lower lobe with temperature of 102° to 103°, and on that date spat about three ounces of blood, and on March 9 another ounce. No blood-spitting thereafter. She spat blood only once previously, namely, on December 6, 1922.

Case 13: Female, aged 34. Early case in condition of apparent cure, working daily for three years. Had two definite colds. First cold began about December 27, 1922, and lasted one week, with principal manifestations in nose and throat, but also with cough and expectoration. The second began February 24, 1923, with elevation of temperature, cough and expectoration and general pains, on account of which she was in bed in a hospital until March 16. Spat blood-streaked sputum on February 26 and 27. Never spat blood before. Subsequent examinations showed no exacerbation of the tuberculosis.

Case 14: Male, aged 30. Early case in a cured condition for seven years, working daily. Cold began February 26, 1923, and was sufficiently severe to put him in bed for four or five days, and off work for a week. Some of the symptoms of the cold continued until March 25, when he had blood-streaked sputum, and then blood-clots for five days. Careful examination inclined me to the diagnosis that the blood-spitting was in association with a relapse of the cold, and was not due to an exacerbation of the tuberculosis. Never spat blood before.

Case 15: Male, aged 41. Moderately advanced case, arrested for two years with no cough, no expectoration, and working daily. Cold began March 2,1923, with considerable cough and expectoration and temperature of 100°. On March 8 considerable blood-spitting in large clots. Spat blood only once before, and then during a cold in February, 1921.

Case 16: Male, aged 48. Far advanced, arrested case, working about four hours a day. Cold began on March 10, 1923, with chills, fever, headache, increased cough and expectoration, and a temperature of 102°. On March 11, temperature of 102.5°; on March 12 sudden hemoptysis of six ounces, according to patient, and sixteen according to family physician; on March 13 another hemoptysis of the same amount, and blood-streaked sputum for five days thereafter. Cold entirely well, and patient out of bed by March 28, with no subsequent symptoms.

Case 17: Male, aged 31. Far advanced quiescent case. Working. April 2 and 3, 1923, blood-streaked sputum in association with increased cough, expectoration and tonsillitis.

2. Twenty cases with the cold in the form of acute bronchitis without blood-spitting

Case 18: Male, aged 20. Early case in condition of apparent cure, working all day. Cold began January 1, 1923, with elevation of temperature which gradually rose to 104° on January 8. There was considerable cough and expectoration. He was entirely well by January 16. Never spat blood.

Case 19: Male, aged 29. Far advanced case in condition of quiescence. On one hour's exercise and six hours' cure. Cold lasted from January 1 to 7, 1923, with much increased cough and expectoration. Never spat blood.

Case 20: Female, aged 59. Far advanced quiescent case, improving rapidly. On January 4, 1923, she developed pain in the back, sore throat and elevation of temperature to 99.4°. These symptoms lasted about two weeks, though it took her about four weeks to become normal. She then developed a gastrointestinal disturbance with pain and vomiting. These symptoms lasted about two weeks, and she remained well thereafter. Has never spat blood.

Case 21: Male, aged 28. Far advanced, progressive pulmonary and laryngeal case. Increase in cough and expectoration January 4, 1923, in association with gastrointestinal disturbance. Never spat blood.

Case 22: Male, aged 59. Far advanced case in condition of arrest, working all day for nine years. Cold began January 8, 1923, with considerable increase in cough and expectoration. It lasted about ten days. No blood-spitting. Spat blood several times during 1914 and once during 1919.

Case 23: Female, aged 52. Consolidation of the whole of the right lower lobe with bronchial breathing and râles. Tubercle bacilli in sputum. Apparently an unresolved pneumonia, which became tuberculous. In good condition, and constantly improving. On all day cure, and one-half hour's exercise. The cold manifested itself by increased cough, expectoration, pains and increase in râles, and lasted from January 21 to February 12. There was no blood-spitting. She spat blood twice before, namely, in June and September, 1922.

Case 24: Female, aged 21. Moderately advanced case in condition of apparent arrest. Developed cold on February 4, 1923, with symptoms in the head and also increase in cough and expectoration. This became entirely well, and the whole train of symptoms redeveloped, apparently in the form of a relapse February 21, with subsidence by February 26. No blood-spitting. One slight hemoptysis in 1919.

Case 25: Female, aged 35. Far advanced case in almost quiescent condition. On four hours' exercise and the rest of the day cure. On February 4, 1923, she developed a severe cold, with inflamed and painful tonsils, markedly increased cough and expectoration; temperature 102°; pulse 148. She returned to her ordinary condition in about two weeks. There was no blood-spitting with the cold. She spat blood several times during the year 1921; also June, 1922.

Case 26: Male, aged 16. Far advanced case, improving. Developed cold on February 8, 1923, with temperature of 100° to 101°, which lasted three days, and increase in cough and expectoration, but without blood-spitting. Two weeks later he had returned to his previous condition. Spat blood twice early in 1922.

Case 27: Male, aged 42. Early case in condition of arrest, working all day. Cold began February 8, 1923, with cough, expectoration and substernal soreness. Was entirely well by February 20, but there was an immediate relapse, lasting for a week longer. No blood-spitting. Spat blood March 1, 1917, May 15, 1918, May 22, 1918, and November 19, 1918, the last three times in association with a cold.

Case 28: Female, aged 32. Early case in condition of apparent cure. Working daily. Cold began February 9, 1923, and lasted until March 25. There was considerable cough and expectoration; no blood-spitting. The cold lasted until she definitely stopped work and went to bed for four days. Cough and expectoration had entirely stopped by March 25.

Case 29: Female, aged 34. Far advanced, arrested case. On February 17, 1923, she developed increased cough and expectoration, with general symptoms and signs corresponding to the epidemic cold, without blood-spitting. She was entirely well two weeks later. She spat blood once in 1912 and once in 1920.

Case 30: Male, aged 20. Moderately advanced case in condition of arrest, working all day. No cough or expectoration. Cold began with cough and expectoration on February 19, 1923, and lasted about a week. No blood-spitting. Spat blood once in July, 1922.

Case 31: Male, aged 37. Far advanced, gradually progressing case, activity slight. Cold began on February 24, 1923, and lasted seven days with elevation of temperature to 102° and increase in cough and expectoration. No blood-spitting. Never spat blood.

Case 32: Female, aged 61. Far advanced, quiescent case, supposed to work about two hours daily, but constantly overdoes it. Cold began March 1, 1923, with increased cough and expectoration, and temperature 101°, which lasted about three weeks; no blood-spitting. Spat blood three times in the past; 1912, frank hemoptysis; 1917, slight once; April, 1921, slight once.

Case 33: Female, aged 46. Early case with never a serious breakdown. Working continuously for sixteen years. Cold began with cough and expectoration about March 15, 1923; duration about three weeks. No blood-spitting. Never spat blood.

Case 34: Female, aged 28. Far advanced, gradually progressing case on account of failure to follow the regimen. Cold began on March 15, 1923, and lasted five or six days with increased cough, expectoration and symptoms of pleurisy, without rise of temperature. No blood-spitting. Spat blood in March, 1921.

Case 35: Female, aged 31. Moderately advanced case, condition of slight activity on account of her continuous overwork. Developed cold December 25, 1922, with evident coryza, increased cough and signs of bladder irritation; temperature elevated slightly; no blood-spitting. The coryza and bladder irritation passed away in a couple of weeks, but the increased cough remained and the expectoration increased, and two months later signs of further tuberculous activity developed. About March 20, a second cold developed with an abscess of each malar sinus which had to be opened. She had no blood-spitting with either cold. Spat blood seven times during the past seven years, each time in association with a very bad cold.

Case 36: Female, aged 24. Far advanced, quiescent case on one hour's exercise and seven hours' cure. Manifested cold from November 20 to 30, 1922, with increased cough and expectoration, no elevation of temperature, no blood-spitting. At this time several members of the family manifested a similar cold. On March 20, 1923, another cold began which lasted ten days, associated with very severe pain in the left side, considerably increased expectoration, almost no increase in cough, no elevation of temperature, and no blood-spitting. Several other members in the family had this cold also. I could not tell which of these two colds was the epidemic cold. Patient never spat blood. On account of my personal opinion that tuberculous patients spat blood with an acute congestion more readily than nontuberculous patients, possibly on account of low blood-pressure, I took the blood-pressure of several non-blood-spitters, thinking it might not be low, but found it low each time; in this case the blood-pressure was 110 systolic, 88 diastolic.

Case 37: Female, aged 37. Moderately advanced case in condition of arrest, working two years. Cold began March 21, 1923, and lasted about three weeks. Its principal manifestations were considerable severe cough, little expectoration and loss of voice. There was no elevation of temperature and no blood-spitting, though she spat blood before in August, 1920, when she had an hemoptysis of six ounces, and in September, 1920, spat blood daily for fourteen days, then had an hemoptysis of several ounces; streaked sputum April, 1921; in December, 1922, in association with a cold, bloody sputum; on October 25, 1922, streaked sputum over one day.

3. Eight cases with cold in the form of acute bronchitis without blood-spitting, followed by an exacerbation of the tuberculosis with blood-spitting

Case 38: Female, aged 42. Very far advanced quiescent case on one hour's exercise, and five hours' cure. Her cold began December 20, 1922, with an elevation of temperature to 100°, some increase in cough and expectoration, but no blood-spitting, though she has had during the past ten years, since I first saw her, several series of blood-spittings, one series in August and September, 1921, being very serious. The cold had apparently subsided by January 20, 1923, when symptoms and signs of slight exacerbation of the tuberculosis began, which continued until March 19. She spat blood on February 12, and also on March 2.

Case 39: Female, aged 35. Far advanced case, gradually improving. Manifested the epidemic cold December 28, 1922, to January 7, 1923, with elevation of temperature to 100°, and considerable expectoration, but no blood-spitting. There was a return of the symptoms from February 10 to March 1, with again a rise in temperature to 100°, increase in cough and expectoration, and bloody sputum three or four different days and two or three times a mouthful of blood; this return of the symptoms appeared to me to be an exacerbation of the tuberculosis. She also spat blood several times in 1921.

Case 40: Female, aged 30. Perfectly well until September, 1922, when severe nervous shock and rapid loss of weight of twenty pounds. A severe cold developed on December 15, 1922, and lasted until January 15, 1923, when she became sufficiently well to be about, but not as well as in the previous summer. March 17, 1923, hemoptysis of four ounces, with blood-streaked sputum the remainder of the day. On March 18, another hemoptysis of four ounces, with a repetition of the blood-spitting. The sputum then became clear until March 28, when she had another day of blood-streaked sputum,followed by chills, slight elevation of temperature and increase in dry cough. Examination on April 4, 1923, the first time I saw her, showed a chronic lesion at the right apex and slight activity at the left. The blood-spitting appeared to me to be due to breaking down, following the lighting up of the tuberculosis by the cold in December and the running down of the previous three months.

Case 41: Male, aged 46. First seen February 1, 1923, with history of bad cold during month of January; in other words, before I saw him. Examination showed moderately advanced case, with chronic involvement of right apex, and scattered active infiltration over whole of left upper lobe without cavity formation. This activity progressed, and on February 15, 1923, patient had an hemoptysis of two ounces, with blood-spitting for twenty-four hours, apparently due to breaking down. On March 24, 1923, while still doing badly, he had another hemoptysis, which the nurse stated to be about five or six ounces, but which he insisted was at least a pint. Examination after this hemoptysis showed a cavity at the top of the left lung which was not evident before, making it practically sure that this hemoptysis was also due to breaking down.

Case 42: Female, aged 40. Far advanced case, gradually improving. Cold began January 10, 1923, with increase in cough and expectoration, and lasted about two weeks; no blood-spitting. About February 1 an exacerbation of the tuberculosis occurred with again increase in cough; and she spat blood-streaked sputum on February 4. She had never spat blood before.

Case 43: Male, aged 24. Far advanced case, improving rapidly. On one-half hour's exercise and seven hours' cure. He developed a respiratory cold January 15, 1923, with increase in cough and expectoration, which lasted only several days. Immediately after he developed apparently a relapse of the cold in the gastrointestinal tract, with pain in the epigastrium, headache, constipation, some vomiting and a rising temperature, which remained at 102° to 103° for two weeks between February 18 and March 4. About February 25 he also developed symptoms and signs of an acute pleurisy over the right lower lobe. He spat blood for three days between February 19 and 22. It appeared to me that this blood-spitting was due to an exacerbation of the tuberculosis with breaking down of tubercles.

Case 44: Female, aged 24. Far advanced case, with the strictest regimen over two years accomplishing little toward cure, but holding the disease almost quiescent. Temperature normal until March 4; then gradual rise to 100.4° with increased cough and expectoration. Temperature elevated eight days. Well for six days. From March 18 to 22, temperature elevated, the highest being 101°, with again increase in expectoration but no increase in cough. Had blood-streaked sputum on March 26, 27, 28 and 29, which appeared to be due to breaking down. She spat blood only once in her life about a year before.

Case 45: Male, aged 49. Moderately advanced case in condition of arrest, working eight years, with occasional petty exacerbations. Well until December 14, 1922, when he was taken with pneumonia with temperature of 102° to 103°, during which I did not see him. Streaked sputum March 31 and April 1, apparently due to an exacerbation of the tuberculosis, in other words, a breaking down of tubercles.

4. One case with cold in the form of acute bronchitis without blood-spitting, followed by an exacerbation of the tuberculosis, also without blood-spitting

Case 46: Female, aged 40. Far advanced, quiescent case, working all day. Very little cough and expectoration. Cold began on January 12, 1923, and she was in bed for ten days. No blood-spitting. Spat blood frequently in the past, namely, in 1906, 1912, 1913, 1914, 1917, 1918, 1919 and 1921. These hemoptyses varied in size from mere blood-spitting to a series of six hemoptyses of six ounces. The cold aroused some activity in the left lung not previously evident, which cleared up rapidly.

While watching for the different cases with colds, five additional were observed with the cold in the form of acute coryza without acute bronchitis, and of these five four manifested blood in the nasal discharge. Personally, I am inclined to believe that the blood in the nasal discharge of these cases is due to an oozing from the congested nasal mucous membrane, similarly to the oozing from the congested bronchial mucous membrane in the other cases with bronchitis. These cases are simply reported, and in no way come into the statistics of hemoptysis.

Case Reports (*continued*)

5. Four cases with the cold in the form of acute coryza, with blood in the nasal discharge

Case 47: Female, aged 23. Far advanced case, rapidly improving, on one and a half hour's walk and all day cure. Cold from February 1 to 10, in form of acute coryza, but also with increased cough and expectoration. The temperature rose to 102°. Occasional blood-streaks from nose, none from the lungs. In 1917 had hemoptysis of sixteen ounces, 1919 another severe hemoptysis, in 1920 and 1922 slight blood-spitting.

Case 48: Female, aged 32. Early case, working all day, never off work due to her tuberculous condition. Cold lasted from about February 1 to 18, with coryza, cough, expectoration, hoarseness and nose-bleed. Spat blood with a cold March 1, 1920.

Case 49: Male, aged 52. Early case in condition of cure. Never had serious symptoms, though had tubercle bacilli in sputum several times in past twenty years. Cold began as acute coryza on March 17 and later patient showed signs of laryngitis and tracheitis. All signs and symptoms had passed ten days later. There was blood in the nasal discharge on the fifth, sixth and eleventh days; no blood-spitting. Spat blood six or seven times during past

twenty years from blood-streaks to a mouthful, the former usually in association with colds, the latter after a protracted period of overwork and possibly due, therefore, to breaking down.

Case 50: Male, aged 42. Far advanced, gradually progressing case, working every day. Cold began March 20, with principal manifestations in the nose in the way of excessive discharge, frequently blood-streaked, slight increase in cough and expectoration. Cold lasted about ten days.

6. One case with the cold in the form of acute coryza without blood in the nasal discharge

Case 51: Male, aged 27. Early case in condition of arrest. Severe cold in head with nasal discharge, without cough or expectoration, beginning January 15, 1923. His principal manifestations were in the middle ear. Never spat blood. No blood in the nasal discharge.

In addition to the cases already detailed, 12 of my patients spat blood without manifestation of a cold, 5 apparently due to breaking down and 7 to unknown causes. They are as follows:

Case Reports (*concluded*)

7. Five cases with blood-spitting due to breaking down, but with no previous signs of cold

Case 52: Female, aged 20. Far advanced case, improving slowly. No symptoms or signs of recent cold. She manifested streaked sputum January 6, February 14, March 17, 18, 29, and April 5, 1923, apparently due to breaking down of individual tubercles. Spat blood also several times during 1922. This breaking down would not necessarily mean advance of the disease, but only the opening up of tubercles or tuberculous masses which nature found impossible to heal without opening. The patient is, undoubtedly, improving not retrogressing.

Case 53: Female, aged 24. Far advanced case, progressing. On January 15, 1923, hemoptysis of two ounces, followed by clots and streaked sputum for a week, and then a two-ounce hemoptysis repeated. Spat blood again on March 28, 1923, apparently due to breaking down.

Case 54: Female, aged 21. Far advanced case, progressing. Blood-streaked sputum on January 28, 1923, apparently due to breaking down.

Case 55: Female, aged 53. Far advanced case, progressing. Blood-streaked sputum over some days beginning March 20, 1923, due apparently to breaking down.

Case 56: Male, aged 41. Far advanced pulmonary and laryngeal tuberculosis in slightly progressive condition, working two and a half months without cough or expectoration. On April 7, 1923, developed pain over right lower lobe; on April 8 profuse expectoration over about an hour, of pus and blood, altogether an ounce to an ounce and a half of blood-tinged pus. Pain practically disappeared, and he felt better almost immediately. Almost no cough or expectoration thereafter. No rise in temperature. Blood-spitting apparently due to breaking down.

8. Seven cases with blood-spitting during these fourteen weeks in which no special cause of the blood-spitting was determined

Case 57: Female, aged 29. Moderately advanced, apparently quiescent case with, in addition, a presystolic mitral murmur, and enlargement of the heart to the left; working. In August and September, 1921, blood-streaked sputum frequently. In December, 1921, spat blood three times without apparent reason. In February, 1922, blood-streaked sputum for two days, in association with coryza and menstruation. In March, 1922, slight blood-streaks once, though no cough or expectoration for several months. In September, 1922, cold with blood-spitting, and this blood-spitting continued almost daily until April 1, 1923. It was

usually in streaks, but mouthfuls were not infrequent. She worked every day. Cause of blood-spitting not determined. She reminds me of an early case (male, aged 30) who spat blood daily, sometimes in streaks, again in mouthfuls, for eighteen months, from April, 1906, to October, 1907. During this time almost every remedy mentioned in the pharmacopoeia in connection with hemoptysis was tried without avail. She has been perfectly well ever since.

Case 58: Female, aged 53. On December 26, 1922, began to spit blood, and spat it almost daily until January 11, 1923, usually in the form of blood-streaked sputum, but sometimes one or two mouthfuls in succession; elevation of temperature to 100°, though ordinary temperature slightly over 99°. Far advanced, gradually progressing case in bed four years, with, in addition, a double mitral murmur and enlarged heart. Since 1918 has had temperature almost always of over 99°, and frequently 100° to 101°. She has spat blood frequently; on September 8, 1919, two ounces; November 25, 1919, blood-streaks in association with a cold; April 30, 1920, eight ounces with streaks the next day, due apparently to breaking down; June 15, 1920, slight blood-spitting in association with a cold; July, 1920, blood-spitting for seven days; October, 1920, slight blood-spitting over several days in association with a cold and a temperature of 102°; November, 1920, blood-spitting almost every day; December, 1920, spat blood frequently up to one-half ounce at a time; January, 1921, spat blood frequently; April, 1921, occasional blood-streaks; May, 1921, considerable blood-spitting, apparently due to breaking down associated with a temperature of 102°; June, 1921, rare blood-streaks; August, 1921, nine days of blood-spitting; September, 1921, blood-spitting for five days; October, 1921, occasional blood-streaks; January, 1922, blood-streaks over twenty-four hours; February, 1922, rare blood-streaks; March, 1922, blood-spitting for three days; April, 1922, blood-spitting for ten days; May, 1922, blood-spitting for three days; July, 1922, frank hemoptysis of four ounces and a number of days of blood-spitting; August, 8, 1922, frank hemoptysis of six ounces with numerous clots thereafter for over a week. No further blood-spitting until December 26, 1922. At the end of May, 1920, she passed four ounces of blood twice daily in bowel movements for seven days. She never passed blood by the bowel before or since. On account of the number of times she has spat blood, and the length of time many of the attacks continued, a number of different remedies have been prescribed, such as digitalis, digitalis and strophanthus, nitroglycerine, both alone and combined with digitalis, atropin, expectorant cough mixtures containing ammonium chloride and aromatic spirits of ammonia, morphine, and calcium lactate; but she has spat blood during them all, and occasionally began to spit blood while taking them. The remedy which she thinks has the most influence in checking the hemoptyses is a combination of tincture of digitalis and tincture of strophanthus.

Case 59: Male, aged 35. Chronic inactive tuberculosis of right apex, unresolved pneumonia of left lower lobe existing over twelve years. Sputum negative for tubercle bacilli on numerous examinations and even inoculations of guinea-pigs. On January 28, 1923, hemoptysis of over eight ounces, with increase in cough and expectoration. Frequent large hemoptyses over the past twelve years, namely, 1911, 1916, 1918, 1919, 1920, 1921, and 1922, the last being on November 30, 1922. The bleeding is usually severe, and lasts from three days to two weeks. The left lower lobe is always dull on percussion, and shows numerous coarse moist râles on auscultation. The cause of the blood-spitting is unknown.

Case 60: Male, aged 21. Early case in a condition of arrest. On January 28, 1923, after a long walk, frank hemoptysis. Also spat blood several times before; in July, 1921, immediately after playing a hard game of ball, hemoptysis of one ounce; August, 1921, frank hemoptysis over five days, altogether about three ounces; June, 1922, following three days strenuous exercise, three days of blood-spitting. Cause undetermined.

Case 61: Male, aged 32. Very early case. The first symptoms of the tuberculosis, namely, mild cough and expectoration, began September, 1922, in association with a cold and never

entirely stopped. Without exacerbation of these symptoms he spat bloody sputum on March 24, 25, 26, 27 and 28. I was inclined to believe that this blood-spitting was due to the present epidemic cold, but because of its vagueness I have put it under the heading of "unknown causation." I saw him first on March 28, 1923. He never spat blood before.

Case 62: Male, aged 35. Moderately advanced case in condition of quiescence, on forty minutes' exercise and all day cure. Without exacerbation of symptoms he spat blood two or three times on February 5 and 6; on March 30 he spat two mouthfuls of blood, and there was blood-streaked sputum for two days. He never spat blood before.

Case 63: Male, aged 22. Far advanced case, improving very slowly. Streaked sputum without other signs or symptoms on April 6 and 7.

DISCUSSION

Epidemic colds are practically surely microörganismal in origin, and bacteriological investigation shows a number of different microöorganisms which appear to be the cause in different colds, like the four or five types of pneumococcus, the streptococcus and Streptococcus hemolyticus, the Staphylococcus aureus, the Micrococcus catarrhalis and the influenza bacillus. Yet epidemics are frequent in which the exact microorganism cannot be determined, either on account of two or three appearing equally numerous in the discharges or on account of no pathogenic microörganism being found. In these latter cases many bacteriologists consider the cause to be a microörganism which is still to be discovered.

With this confusion in regard to colds it is not surprising that we do not know at the beginning of an epidemic cold among tuberculous cases whether it is likely to be associated with blood-spitting or not, but it is possible that a study of blood-spitting in association with colds may help in the differentiation of colds in general.

Experience shows that not all epidemic bronchopulmonary colds carry with them a similar predisposition to blood-spitting. The researches at the Phipps Institute make it appear possible that colds produced by the pneumococcus are more frequently responsible than colds produced by other microörganisms. It is not impossible, however, that the influenza bacillus and some other microörganisms may carry with them a similar capability.

Lay people believe that patients with tuberculosis of the lungs are particularly susceptible to respiratory colds. This as well as other studies that I have made point to the fact that they are less susceptible than ordinarily well people. During the fourteen weeks from January 1 to April 7, 1923, I saw 204 patients with tuberculosis; of these, 51 (25 per cent) manifested the cold. A survey of sixty personal healthy friends of 12 entire families during the same time showed 42 (or 70 per cent) with the epidemic cold.

This corresponds with my experience (4) during the influenza epidemic. In General Hospital No. 17 we had a population of three hundred, 200 being tuberculosis patients and 100 ordinarily healthy doctors, nurses and corps men. Of the 200 tuberculosis patients 3 (1.5 per cent) manifested the disease; of the 100 healthy persons, 28 (28 per cent); in other words, nineteen times as many healthy people manifested it as those who were tuberculous. It also corresponds with my personal experience (5) of lobar (pneumococcus) pneumonia which appears to be less frequent among the tuberculous.

The probable reasons for the greater immunity of the tuberculous are: *1.* Tuberculosis patients under treatment are on rest or considerable rest, on a high quality nourishment, and are living in the open air. On account of this regimen the physiological activities of the body are nearer perfection than in a healthy individual working hard in the pursuit of a living. *2.* One bacterial infectious disease aids in the exclusion of a second. For instance, even when scarlet fever and measles are simultaneously epidemic, we rarely see the two occur in the same individual simultaneously. Epidemics of scarlet fever, diphtheria, and typhoid fever are almost unknown in tuberculosis sanatoria, and a case of smallpox has very rarely, to my knowledge, been reported in association with tuberculosis.[1]

Because blood-spitting is frequently caused in tuberculosis patients by an acute congestion due to a cold does not mean that it may occur in nontuberculous patients due to the same cause. Blood-spitting, though not pathognomonic of tuberculosis of the lungs, is very suspicious, because apparently healthy people do not manifest it in association with acute bronchitis. It is possible that the usual low blood-pressure in tuberculosis patients may allow oozing more readily than in the ordinary or high blood-pressure of the nontuberculous.

SUMMARY

During the fourteen weeks of the epidemic of cold, lasting from January 1 to April 7, 1923, I saw altogether 204 tuberculosis patients. Of these, 51 (25 per cent) manifested the cold; 46 (90 per cent) in the form

[1] In a very valuable paper by Howk and Lawson (AMERICAN REVIEW OF TUBERCULOSIS, 1920, iv, 490) the authors mention the rarity of the occurrence and paucity of reports in the literature, and then give a very complete account of an epidemic of smallpox at the Metropolitan Life Insurance Company Sanatorium in 1914, when seven of the patients with pulmonary tuberculosis contracted smallpox.

of acute bronchitis, and 5 (10 per cent) in the form of acute coryza. Of the 46 with bronchitis, 17 (37 per cent) spat blood in association with the bronchitis, and 8 later with an exacerbation of the tuberculosis; of the 5 with coryza, 4 (80 per cent) had blood in the nasal discharge.

Altogether, 37 of these 204 patients spat blood during these fourteen weeks, divided as to possible causation as follows:

Blood-spitting associated with acute bronchitis	17
Blood-spitting associated with exacerbation of the tuberculosis	8
Blood-spitting associated with no definite cause	12
Total	37

In the seven weeks previous to January 1, and in the seven weeks succeeding April 7, in other words, fourteen weeks or a similar period to the one I am reporting, I saw 220 tuberculosis patients; of these, 13 spat blood, or only one-third the number that spat blood during the epidemic.

A previous study of 321 patients who died of tuberculosis showed that 60 per cent of them spat blood at some time. The same study showed that the average length of life from the time the diagnosis was made, in other words, from the beginning of evident clinical symptoms till the time of death, was eighty months. Or, putting it another way, in the eighty months preceding death 60 per cent of patients spat blood.

Comparing the 204 patients of the present series with this 321, we would expect 60 per cent, or 120 of them, to spit blood in eighty months (348 weeks), or five in fourteen weeks, but since some patients spat blood more than once, we would expect the actual number to be greater than five. The study of all my patients over fourteen weeks, apart from the epidemic, (seven weeks before and seven weeks after) showed that 13 (6 per cent) spat blood under these ordinary circumstances, while 37 (18 per cent), or about three times the number, spat blood during the epidemic.

In the epidemic reported by Montgomery, extending over twenty-one days in the Chestnut Hill Home for Consumptives, 14 out of 66 patients, or fifteen times more patients, spat blood than would be expected over this short length of time; taking short periods out of our duration of fourteen weeks we find at one time 9 patients spitting blood in eleven days (or six and a half times the expected number), and again another series of 11 patients in seventeen days (or five times the expected number).

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THE EARLY LESION OF INTESTINAL TUBERCULOSIS IN EXPERIMENTAL ANIMALS AND MAN[1]

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The early lesion of intestinal tuberculosis has not, so far as we can find, been thoroughly studied. We have been unable to find in the literature any work recording such observations in man or animals. Aschoff (1) states that the earliest lesion is a small tubercle, the size of a millet seed, situated in the mucosa and extending into the submucosa. This tubercle has a caseous centre and is found most commonly in the region of a lymph follicle. Such lesions can be seen with the naked eye.

It is the consensus of opinion that tubercle bacilli are carried through the intestinal mucosa during the normal process of digestion, that they leave no trace of their entrance, and that the first pathological changes seen are in the lymph nodes situated along the natural paths of drainage. There is no doubt that children are affected through the drinking of milk from tuberculous cows, and yet very often no intestinal lesions can be seen. There is no question that tubercle bacilli get through the lymphatics of the intestine without any ulceration being left behind, as far as can be ascertained by gross examination. Aschoff (2) states that the great power of absorption of the intestine for tubercle bacilli has been confirmed experimentally. A greater certainty exists in regard to the actual disease. Here the primary intestinal tuberculosis retreats in favor of the secondary lesions.

Freeman (3) has called attention to the fact that tabes mesenterica is often due to tuberculous infection.

Webb, Ryder and Olcott (4) found the mesenteric lymph nodes involved in 19 out of 31 tuberculous guinea pigs that had been infected subcutaneously. Of these, 27 showed gross tuberculosis of the liver and all had tuberculosis of the hepatic lymph node.

Redman (5) claimed that in every instance in which he fed virulent tubercle bacilli to guinea pigs, the mesenteric lymph nodes became involved in 34 to 41 days. There were tuberculous nodules in the cecum

[1] From the John Rogers Hegeman Memorial Laboratory, Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York.

and colon at 81 to 86 days. He stated that the distribution of intestinal tuberculosis in the guinea pig does not differ greatly from the same disease in the human being. No microscopic study of the intestine is reported.

Nicolas and Dergas (6) fed large numbers of tubercle bacilli mixed with bread and milk to dogs which had been starved 24 to 36 hours. The dogs were killed 3 to 3½ hours after the feeding. Chyle was collected from the thoracic duct and the cisterna. Inoculation of the chyle into normal guinea pigs proved that the chyle from 2 out of 6 dogs contained tubercle bacilli.

LeNoble (7) quotes the work of Chauveau, Gerlach and Dobroklovski in which they demonstrated that tubercle bacilli easily penetrated the normal intestinal mucosa without apparent lesion. The work of Prevost is cited, in which he noted that the bacilli reach the intestine in three ways: (1) most commonly by the digestive tract, (2) next by the blood, and (3) least frequently by the lymphatics. LeNoble believes the ulceration in the intestine to be due to bacillary emboli which lead to infarction and resultant necrosis.

Fried (8) has noted the common occurrence of tubercle bacilli in the feces of human patients with open pulmonary tuberculosis. Of 103 cases with positive sputum 98 had tubercle bacilli in the feces as determined by guinea-pig inoculation.

Calmette (9) states that it is a well-established fact that many bacteria in the circulation may be eliminated through the intestine. He cites the work of several authors, that of Hess being the most striking. A point to be considered in all of the experiments quoted is that actively motile bacilli were used in each instance.

We have noted the regularity with which the mesenteric lymph nodes are involved in guinea pigs dying from generalized miliary tuberculosis. In practically all of the animals there has been hepatic tuberculosis which varied from slight to extensive involvement of the entire organ. The hepatic lymph node in all such cases has shown tuberculous involvement. In our study of tubercle bacilli in the bile (which will be reported in a separate paper) we have found it the rule to find tubercle bacilli in cases of hepatic tuberculosis. From this observation one can readily see that there is a more or less constant feeding of tubercle bacilli into the intestine from the liver.

With these facts in mind, we have made careful examinations of the entire intestinal tract of several animals in search of evidence of lesions.

Our experience was the same as that of most laboratory workers, for we found no ulceration nor anything that would suggest tubercle formation. There was no doubt about the presence of tubercle bacilli within the lumen of the intestine and of tuberculous lesions in the mesenteric lymph nodes. The most logical explanation of the transportation of the bacilli from the former to the latter was by the natural lymph current, as all lymph currents are centripetal unless there is obstruction. The question which arose and did not seem answered was, "Could the tubercle bacillus, a nonmotile microöganism, a foreign body, be swept through the intestinal mucosa without any reaction on the part of the host?"

EXPERIMENTAL

Following the observations of Aschoff that the earliest lesion in the human intestine is in the region of the lymph follicles, we decided to make serial sections of a number of the lymphoid collections in the large and small intestines of a number of the guinea pigs which showed no gross lesions of the intestines and still had hepatic and mesenteric lymph-node tuberculosis. The report of our findings is given below.

Eight guinea pigs which had been subcutaneously infected with human tubercle bacilli, H37, were taken. One of these pigs (68) showed several ulcers in the cecum and ascending colon which were typical tuberculous ulcers. The other seven showed no gross lesions, aside from what appeared to be prominent lymphoid tissue in one or two of them. Eight to twenty areas of lymphoid tissue were taken from every case except one (62). The length of life of the guinea pigs varied from 65 to 145 days. In every case sections were made of the liver, hepatic lymph node and mesenteric lymph nodes. The result of our findings are seen in table 1.

From table 1 it will be seen that 7 of 8 guinea pigs showed lesions and bacilli in the intestinal tissue and all showed lesions and bacilli in the liver, hepatic node and mesenteric nodes. The reason for our failure to find tuberculous lesions in guinea pig 62 was undoubtedly the fact that we took only what appeared to be two small erosions and failed to take numerous areas of lymphoid tissue, as in the other animals.

Having serial sections, we were able to follow the entire lesion. In every instance we found the lumen of one or more intestinal glands, usually more, containing moderate to extensive inflammatory exudate which consisted of polymorphonuclear and endothelial leucocytes. The

large majority of the glands were normal. In the great majority of those which contained the inflammatory exudate we found tubercle bacilli, sometimes in small numbers, at other times in considerable numbers. No tubercle bacilli could be found in the normal glands. The glands which contained the inflammatory exudate were invariably those which dipped farthest into the lymphoid tissue; in other words, those which had the poorest drainage. In most instances the tubercle bacilli found were

TABLE 1

GUINEA PIG NUMBER	LENGTH OF LIFE	INTESTINE		LIVER		HEPATIC NODE		MESENTERIC NODES	
		Gross	Microscopic	Gross	Microscopic	Gross	Microscopic	Gross	Microscopic
	days								
60	122	Hyperplastic lymphoid tissue	Pos.	Ext.	Pos.	Ext.	Pos.	Ext.	Pos.
44	81	Neg.	Pos.	Ext.	Pos.	Ext.	Pos.	Ext.	Pos.
35	145	Neg.	Pos.	Mod.	Pos.	Ext.	Pos.	Mod.	Pos.
68	66	Ulcers in cecum and colon	Pos.	Ext.	Pos.	Ext.	Pos.	Ext.	Pos.
69	72	Neg.	Pos.	Mod.	Pos.	Mod.	Pos.	Sl.	Pos.
62	110	Two small erosions of ascending colon	Small ulcers. No evidence of tuberculosis	Ext.	Pos.	Mod.	Pos.	Mod.	Pos.
36	131	Hyperplastic lymphoid tissue	Pos.	Ext.	Pos.	Ext.	Pos.	Mod.	Pos.
57	141	Neg.	Pos.	Mod.	Pos.	Mod.	Pos.	Sl.	Pos.

Neg.: No pathological changes seen.
Sl.: Slight changes.
Mod.: Moderate changes.
Ext.: Marked changes.
Pos.: Lesions and bacilli found.

phagocytosed. In several instances in which the bacilli were numerous we found typical tubercle formation with necrosis of the exudate in the central portion within the lumen of the gland.

Most of the glands containing the inflammatory exudate showed no evidence of break in the epithelial lining. In a few having extensive inflammatory exudate and numerous bacilli, erosion of the lining epithelium was found, which varied from a slight to an extensive lesion. When the erosion of the glandular epithelium was present the submucosal lesion was always more extensive.

The most marked inflammatory reaction in the submucosa was directly underlying the glands having inflammatory exudate within their lumen. In these areas bacilli were always found without difficulty, generally being more numerous than in the gland exudate. In the early lesions there was no necrosis. In the older lesions small areas of necrosis were invariably present. In the large majority of instances there was no evidence of ulceration of the overlying mucosa.

In some cases the majority of lymphoid collections showed lesions. In other instances only 1 or 2 areas showed involvement. Lesions were found in both the ileum and large intestine, but more frequently in the cecum and ascending colon. In the majority of instances the lesions were confined to the area of lymphoid tissue, largely because there was poorer drainage of the glands in these regions. A few small lesions were found not associated with the lymphoid collections.

In all cases the severity of the lesion in the mesenteric lymph nodes paralleled the extent of tuberculous involvement of the intestine. To a large extent the amount of involvement of the intestine corresponded fairly closely with the degree of tuberculous infection of the liver.

Careful search for vascular bacillary emboli was made in many of these lesions, but no evidence was found even in lesions where there were several areas of necrosis. In all probability some of these intestinal lesions would have undergone ulceration had the guinea pigs lived for a longer time. From our study it would appear that the ulceration is not due to infarction as claimed by LeNoble, but rather to necrosis resulting from the tubercle bacilli being carried to the submucosa after being phagocytosed in the lumen of the glands or as a result of the extensive inflammatory exudate within the glands. In other words, the necrosis and later ulceration in the intestine are brought about in the same way that the same condition is produced in other organs of the body.

After careful study of these microscopic tuberculous lesions of the intestine, we are led to believe that the following is the sequence of development of intestinal and shortly later mesenteric node tuberculosis: In the case of the guinea pig, tuberculous lesions in the liver ulcerate into the biliary system and bacilli are discharged with the bile into the intestine. We have a more or less continuous flow of the bacilli into the intestine from this time to the death of the animal. In passing down the intestine some of these bacilli become lodged in the lumina of the intestinal glands. If not dislodged they will cause an inflammatory exudate

with resultant phagocytosis. Thus phagocytosed they are carried back into the wall of the intestine where lesions will develop. As the lymphatics of the intestine are large and very open, it is quite likely that some of the leucocytes will wander into them and soon be carried to the lymph node in direct line of drainage without much delay in the submucosa of the intestine. If this happens one would not be surprised to find tuberculous lesions in the node as early as in the intestine.

It is a well known fact that in the guinea pig local lesions can heal and lymph nodes recede when tubercle bacilli cease to be fed into them from a peripheral focus. Should it have been possible to stop the pouring of tubercle bacilli into the intestine from the liver in these animals that we have studied and to have prolonged their lives, undoubtedly most of the lesions seen would have healed without leaving any microscopic trace behind, except perhaps for a slight amount of fibrosis in the submucosa. While generalized tuberculosis has been developed in the guinea pig by feeding the animals tubercle bacilli, nevertheless no one has been able to produce ulceration with any degree of constancy. Undoubtedly small local lesions developed in the intestine in every case, but when the bacilli were no longer fed the local lesions healed.

HUMAN LESIONS

Since the completion of the study of the intestinal lesions of tuberculosis in the guinea pig, we have been fortunate in securing specimens of tissue from a human case. The autopsy and histological findings are here recorded:

Case N: Clinical symptoms for about two years before death. Clinical findings were far advanced pulmonary tuberculosis, with cavitation and obliteration of pleural cavities. There were no intestinal symptoms. At autopsy, 2 hours postmortem, very extensive tuberculosis of both lungs with cavitation and obliteration of both pleural cavities was found. The right heart was dilated. A few tubercles were found in the spleen. Aside from congestion, the liver, kidneys, adrenals, stomach, large intestines and pelvic organs appeared normal. In the ileum, scattered through its entire extent, were found a considerable number of nodules from pin-point to pin-head size. Some of these appeared yellowish, others rather translucent. A very few of the larger nodules showed a small depression in the central portion, which suggested early ulceration. There were no typical tuberculous ulcers. In the proximal portion of the appendix two similar lesions were found. Neither of these was ulcerated. Microscopically, the heart was normal. There was very extensive caseation of the lungs. Tubercle bacilli were found, but were scarce. Small tubercles were in the spleen and liver. The kidneys, adrenals and pelvic organs showed no evidence of tubeculosis in the few sections examined.

Eight pieces of ileum with the smaller nodules were serially sectioned, some 4,000 sections being obtained. Microscopically, these eight portions of the intestine showed 10 separate

tuberculous lesions. Of these, 3 showed microscopic ulceration and 7 showed no ulceration. Tubercle bacilli were found in the submucous tissue in all the lesions. The bacilli were scarce, averaging less than one bacillus per section in some 50 sections examined very carefully. In 8 of these lesions inflammatory exudate, consisting largely of polymorphonuclear leucocytes, was found in from one to six separate glands over the tuberculous lesion. The remaining glands all appeared normal. Three of these 8 lesions showed early ulceration of the mucosa; 5 showed no ulceration in any portion. No tubercle bacilli were found in the exudate in the glands examined. Judging from the scarcity of the bacilli in the submucous lesion, it would be mere chance to find a tubercle bacillus in the relatively few sections of glands with inflammatory exudate examined.

A point of interest in the lesions in this case is that the two which showed most extensive caseation in the submucous lesion showed no necrosis of the mucosa in any portion. Aschoff states that the ulceration in tuberculosis of the intestine is the result of these areas of caseation breaking through the mucosa. In the 3 lesions here studied in which early ulceration was present there was but little caseation. The inflammatory reaction of these lesions was of a more acute type, the polymorphonuclear leucocyte being the preponderant type of cell present. From this it would appear that caseation *per se* is not necessarily the essential factor in ulceration.

Another point of interest is that the lesions which showed the most caseation showed no inflammatory reaction in the overlying glands. In all probability the primary point of inflammation disappeared following the carrying of the bacilli or bacillus into the submucous tissue, so that no evidence was left of the point of primary infection. These two lesions also support a reasonable assumption that the inflammatory exudate in the glands is a result of tubercle bacilli becoming lodged in them.

This case corresponds very closely with the description given by Aschoff of the early lesions in intestinal tuberculosis. His microscopic picture parallels very closely the picture above presented of the early tuberculous lesions in the guinea-pig intestine.

While undoubtedly we have in this case comparatively early tuberculous lesions, still the earliest is not found. Such a lesion would be found only by accident, for it would not be visible to the naked eye. The lesions here seen, however, allow a fairly clear conception of what the earlier lesions would be. It seems logical that the deductions relative to early tuberculosis in the guinea-pig intestine apply equally well to the lesion in the human intestine.

One does not question the fact that, even in secondary intestinal tuberculosis in the human being, it takes a long time of "feeding" with

sputum before ulceration occurs. Undoubtedly much early intestinal tuberculosis escapes gross detection. The reason why the record of the early lesion of intestinal tuberculosis has not heretofore been made is undoubtedly due to the fact that it has been generally felt that it ought to be large enough to permit detection by the naked eye.

SUMMARY

The above report represents the observations on something over 100 portions of the intestine and the examination of approximately 30,000 sections, many of them carefully studied for the presence of tubercle bacilli. Serial sections were made of all the lesions and it is because of this technique that we were able to arrive at a logical understanding of the development of the tuberculous lesion in the intestine.

A criticism which may justly be made of this work is that the series of guinea pigs reported is small. Because of the work involved in serial sections, the series must necessarily be small. We feel that sufficient evidence was obtained from this small series, thoroughly worked up, to justify our deductions.

We regret the fact that only one human case could be reported. Early intestinal tuberculosis is not commonly seen at best. The case here reported, however, corresponds so closely to a similar condition in the guinea pig that it seems logical that the development of the lesions in both is very similar.

A point relative to the interpretation of the early tuberculous lesion in the intestine, which may justly be raised is, "Could not the inflammatory reaction within the lumina of the glands be secondary to the tuberculous lesion in the submucosa?"

There are two points which make this interpretation seem to us illogical. The first is that in the areas where the tuberculous lesions were present in the submucosa the large majority of the overlying glands appeared normal, as did all of the glands not in association with a tuberculous lesion. There were, however, practically always a few glands, having inflammatory exudate in their lumina, present in all tuberculous lesions, and the greatest amount of lesion in the submucosa lay adjacent to these glands. One was able to demonstrate tubercle bacilli in these glands in practically every instance, being often most numerous in the centre of the exudate. It seems illogical to us that the inflammatory exudate should be restricted to such a few glands if it had been secondary to the submucous lesion.

The second point is that the cells of inflammation are attracted chemotactically toward the infectious agent. One does not question the fact that they migrate away from the parent lesion considerably, but it hardly appears logical that these cells should very largely congregate in two or three glands and leave the rest of the glands uninvolved.

CONCLUSIONS

1. The early tuberculous lesions of the intestine in the human being and guinea pig are described. These appear identical in their mode of development.

2. If tuberculous peritonitis is ruled out, tuberculosis of the mesenteric lymph nodes means that there are or have been tuberculous lesions in the intestine.

3. Caseation is not a necessary factor in the production of ulceration. No evidence of bacillary emboli was found.

4. There is no evidence that tubercle bacilli are "swept through" the intestinal mucosa during the process of normal digestion.

5. There is evidence that an inflammatory exudate exists in the lumina of the intestinal glands in the large majority of early tuberculous lesions. It seems reasonable that this is a precursor to the finding of bacilli in the submucosa and later in the mesenteric lymph nodes.

6. Evidence is presented that tuberculous lesions exist in the intestine when there is no gross manifestation of the lesions.

7. Intestinal tuberculosis is common in guinea pigs having generalized miliary tuberculosis.

8. Tuberculous ulcers may occur in the guinea pig but they are rare.

9. Hepatic tuberculosis acts as a "feeder" for intestinal tuberculosis in the guinea pig.

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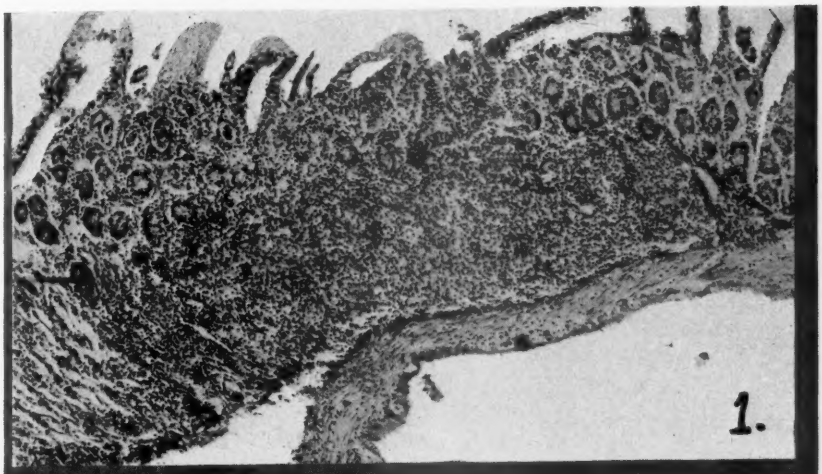
Tubercle bacilli demonstrated in all lesions

FIG. 1. Very early tuberculous lesion in small intestine of guinea pig 36. No ulceration and slight inflammatory reaction in lymphoid tissue of a Peyer's patch. Note inflammatory reaction in lumina of glands in upper right hand corner. All of the rest of the glands over the entire lesion normal. × 65.

FIG. 2. Higher power of fig. 1, showing glands filled with inflammatory exudate. × 275.

FIG. 3. Solitary tubercle in fold of mucosa of large intestine in guinea pig 36. No ulceration. No inflammatory reaction in any glands except the one below and to the left of the area of necrosis. × 35.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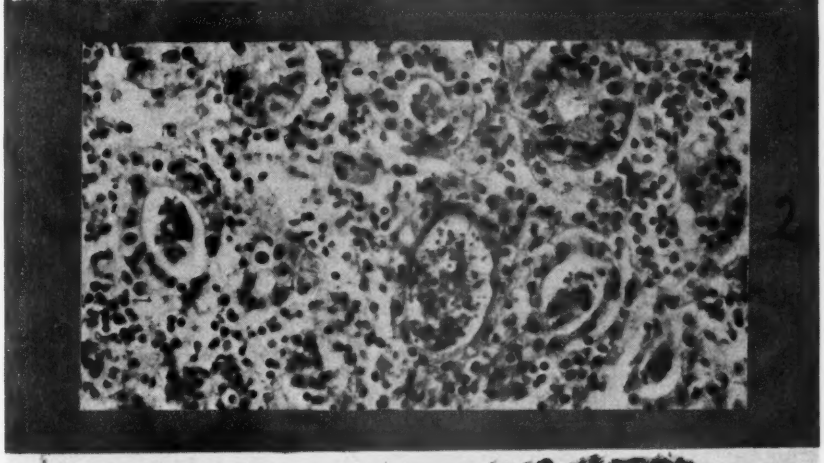
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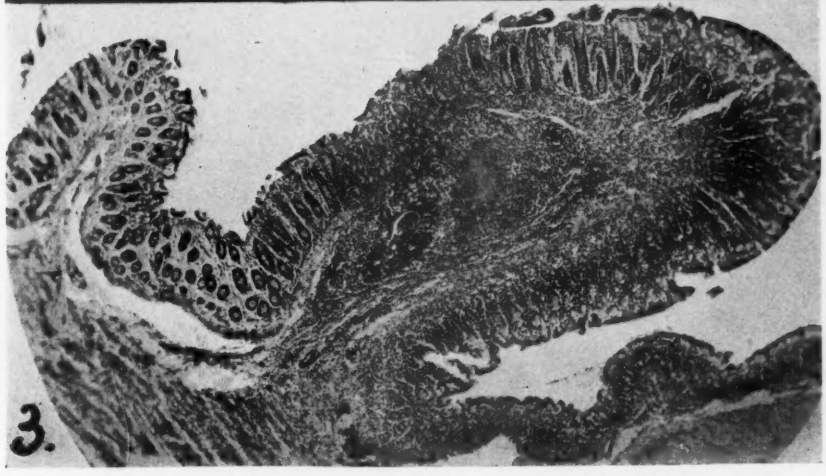
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FIG. 4. Section of lymphoid tissue in large intestine of guinea pig 44. Glands all normal except two large ones shown in picture. One is filled with inflammatory exudate, the other with mucus. Tubercle bacilli in inflammatory exudate in gland and in tissue below and to the left of the gland. Aside from this small area no tubercle bacilli could be found. No other lesion in the entire area of lymphoid tissue in either mucosa or submucosa. × 65.

FIG. 5. Group of tubercle bacilli found in gland at left of fig. 6. Ziehl-Neelsen stain. × 1800.

FIG. 6. Section of lymphoid area in cecum of guinea pig 36. Note absence of necrosis. A gland at either side (note their position) is filled with inflammatory exudate. Those in the middle are normal. The dark areas in the centre represent all that is left of the normal lymphoid tissue. No tubercle bacilli could be found in this region. The rest of the submucosa shows extensive inflammatory reaction, practically no necrosis and numerous bacilli found. × 30.

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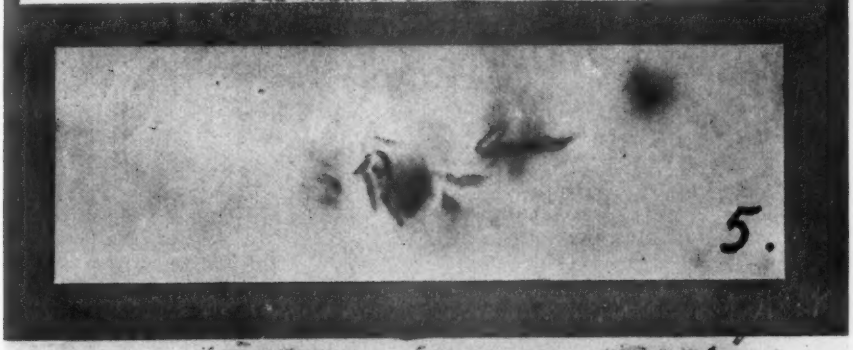
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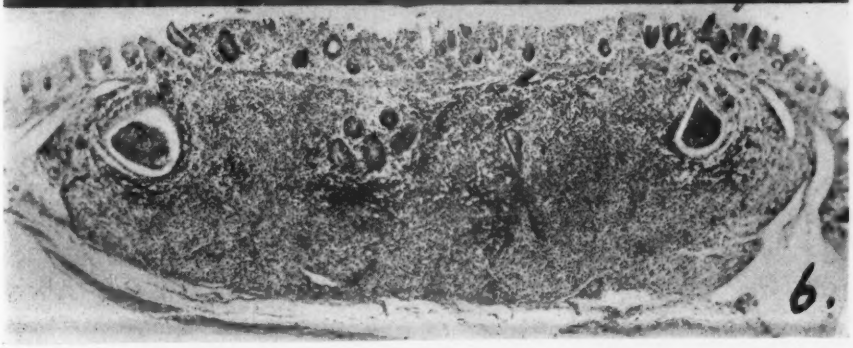
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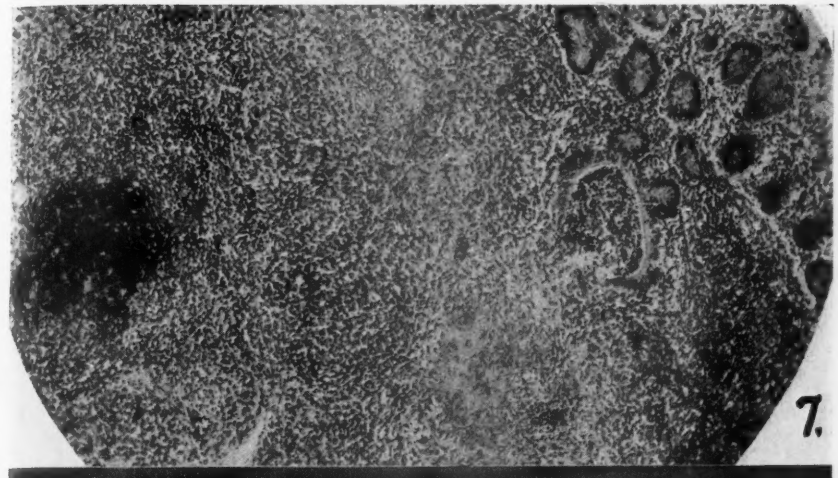
FIG. 7. Section of lymphoid tissue in cecum of guinea pig 69. Note gland distended with inflammatory exudate, and necrosis of epithelium in lower left hand corner of gland. Extensive necrosis shown in tissue "fed" from this gland. × 75.

FIG. 8. Later stage of ulceration in large intestine of guinea pig 68. There is no ulceration except in the gland involved in central portion of picture. × 20.

FIG. 9. Advanced ulcer in large intestine of guinea pig 68. All of area of lymphoid tissue destroyed. Entire wall of intestine destroyed. Defect filled with tuberculous granulation tissue. Note tuberculous lesion in submucosa to left of ulcer. × 20.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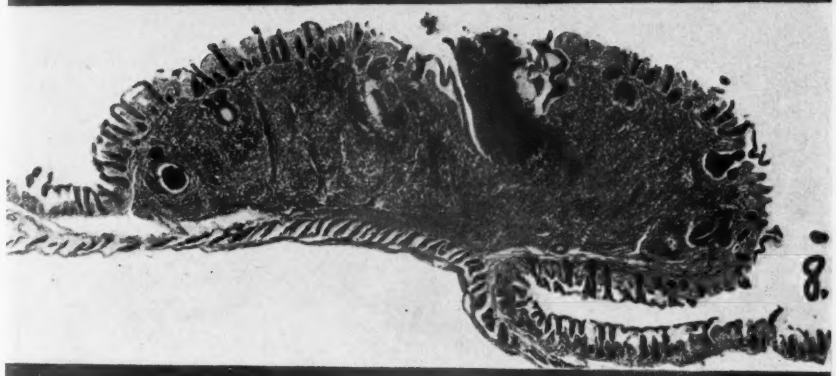
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FIG. 10. Sections of early tuberculous lesion in human small intestine. No ulceration in any portion as shown by serial section. All but three glands normal. Three glands show marked inflammatory exudate into the lumen. × 60.

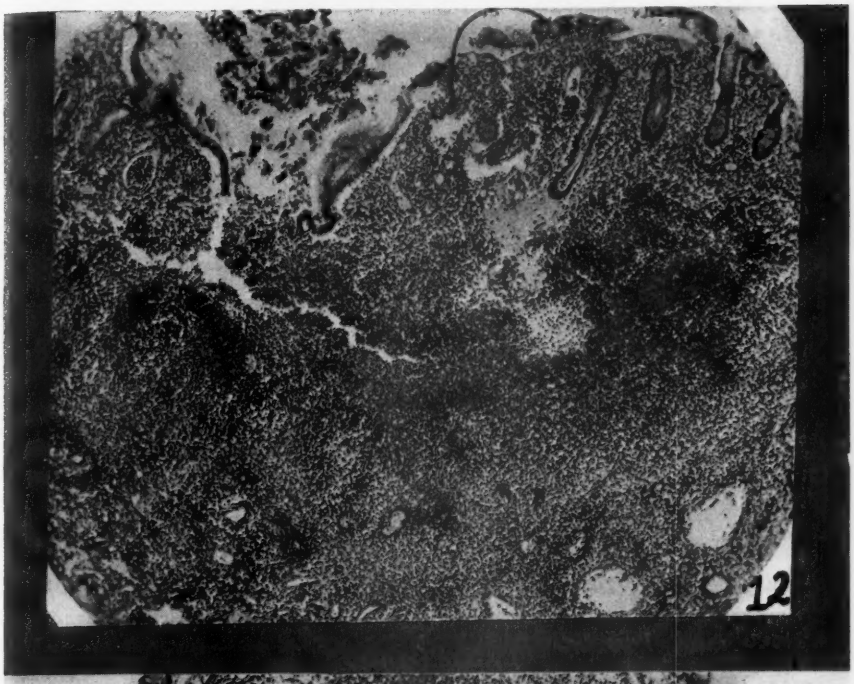
FIG. 11. Higher power of glands involved in fig. 10. Note leucocytes in migration through wall of gland on lower end of central gland. × 175.

10.

11.

FIG. 12. Lesion in human small intestine showing early ulceration. Ulceration evidently started in one of the glands dipping into the submucosa. Note the marked inflammatory reaction in submucosa and the absence of much caseation necrosis. × 50.

FIG. 13. Lesion in human small intestine. Shows caseous tubercle in submucosa. No ulceration of mucosa in lesion as shown by serial section. No inflammatory reaction in any glands overlying the lesion. Probably original small inflammatory focus has disposed of the tubercle bacilli and then disappeared, leaving no trace behind. × 75.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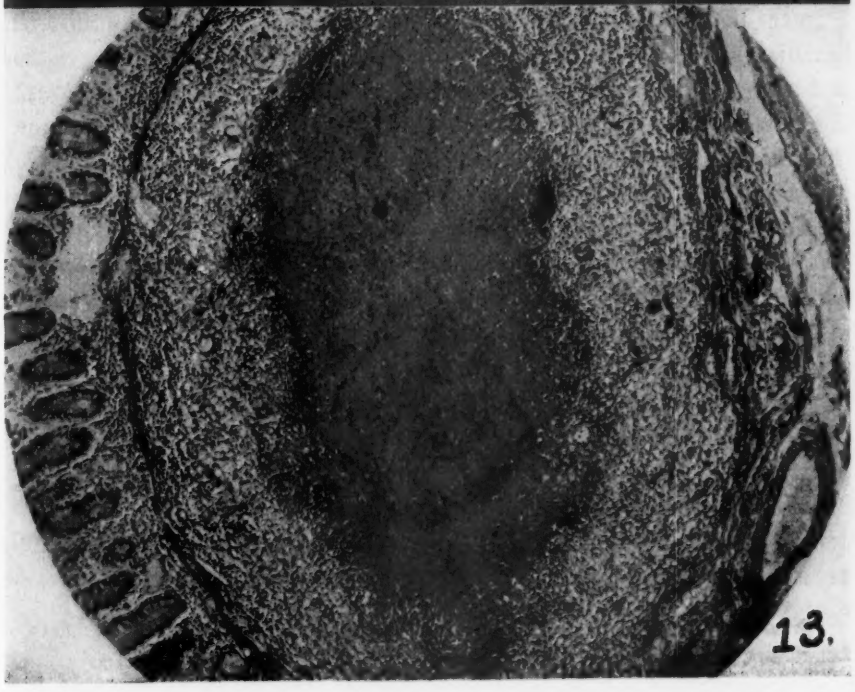
13.

EXPERIMENTAL RENAL TUBERCULOSIS[1]

WITH SPECIAL REFERENCE TO EXCRETORY BACILLURIA

E. M. MEDLAR AND K. T. SASANO

There is at present a difference of opinion regarding the significance of tubercle bacilli in the urine, especially as to the presence or absence of renal tuberculosis. Even when genital tuberculosis is carefully ruled out, there remain some cases, without any clinical signs or symptoms and with an apparently normally functioning kidney, in which tubercle bacilli are found in ureteral urine. Such findings have led to the belief that tubercle bacilli are excreted through a normal kidney without tuberculous lesion in the kidney tissue, the term "excretory bacilluria" being used to signify this condition. The work below reported was undertaken to get a clearer understanding of the facts of the case in experimental animals.

In the past there have been ascribed three routes by which the tubercle bacilli may reach the kidney; namely, hematogenous, lymphogenous, and ascension through a dilated ureter. At present there is an increasing conviction that the hematogenous route is by far the most common, the other routes being exceedingly rare at best. It is extremely doubtful whether the bacilli ever reach the kidney by way of the lymphatics.

Beer states that tubercle bacilli may be brought to the kidney from a distant focus in the body and the bacilli may be excreted in the urine without there being a tuberculous lesion in the kidney, although in the majority of cases the bacilluria means tuberculosis of the kidney. He states, however, that much of the work done on excretory bacilluria is worthless because it lacks the completeness of careful scientific work and that much of the best work is partly contradictory.

Smith believes that, with a tuberculous lesion anywhere in the body, it is reasonable to suppose that frequent temporary bacillemia may occur and that it has been shown that tubercle bacilli can be excreted through healthy kidneys. He states that surgery is the only hope of a cure in

[1] From the John Rogers Hegeman Memorial Laboratory, Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York.

renal tuberculosis, for there is no authentic case on record of spontaneous healing of a tuberculous kidney.

Ekehorn in his excellent article states that, in the greater number of cases of renal tuberculosis, the earliest sign is the microscopic morbid change of the urine, which contains pus cells, generally some blood, and usually tubercle bacilli. These findings in the urine follow the latent stage of the disease when the infection breaks through into the pelvis of the kidney. He found it easier to demonstrate tubercle bacilli in the urine in a comparatively early stage of the disease. At this stage tubercle bacilli can be demonstrated in 80 to 90 per cent of the cases. The finding of the tubercle bacillus is the only pathognomonic sign. Guinea-pig inoculation may have to be resorted to repeatedly, to establish the presence of tuberculous infection. He believes that in case the guinea-pig inoculation is positive the possibility of an elimination bacilluria should be borne in mind, especially if there is active tuberculosis in some other part of the body.

Hobbs reports 1,000 autopsies on cases dying from pulmonary tuberculosis. In 16.2 per cent there was a clinical record of tuberculous lesions of the kidney. He examined a small series of kidneys from these cases, and found that 32 per cent showed microscopic tuberculosis when only 18 per cent showed macroscopic lesions. Symptoms of renal tuberculosis had been present during life in only a small percentage of the cases studied. In conjunction with Gloyne and Page he inoculated the urine from 100 cases, none of which showed any symptoms of genitourinary tuberculosis, into guinea pigs. Six positive results were obtained. One of these cases came to autopsy, and careful microscopic examination failed to reveal any evidence of renal tuberculosis. Because of this finding the author concludes that the finding of tubercle bacilli is not necessarily proof positive of genitourinary tuberculosis.

Foulerton and Hillier reported 18 cases of tuberculosis which had tubercle bacilli in the bladder urine in 9 cases. At autopsy 6 of these 9 cases showed no tuberculosis of the genitourinary tract.

Kielleuthemer reported 13 cases of advanced pulmonary tuberculosis which had albumin-free urine, with negative guinea-pig inoculation in all cases. In 11 cases having albumin in the urine and no tuberculosis in the genitourinary tract at autopsy 3 gave positive guinea-pig inoculation. He concludes that tubercle bacilli do not pass through a normal kidney, but may occasionally pass through an impaired kidney without any tuberculous lesion in the kidney.

Hyman and Mann state that occasionally an excretory tuberculosis may account for the presence of tubercle bacilli in the urine. They quote the reports of Loumeau, Wildbolz and Von Rijssel to substantiate this claim. Barney in discussing this paper states that tubercle bacilli are found in the urine from healthy kidneys.

Geisinger believes that the kidney is an excretory organ for bacteria, comparable to the liver. Germs are probably being fed constantly into the blood-stream from various sources, and are carried to these organs for excretion. It is possible for this elimination to occur without any damage to the kidney itself.

Brown states that tubercle bacilli can be excreted through apparently normal kidneys without injury to the kidney. Of 104 cases 10 per cent gave positive guinea-pig inoculation with urine sediment. Of this 10 per cent he states one or more may have had renal tuberculosis. Brown quotes Bertier as believing that bacilluria can occur without renal change. He also states that it appears to be settled that tubercle bacilli can be excreted by the kidney without any damage being done to the kidney.

Churchman, in going over the records at the Johns Hopkins Hospital of cases of generalized miliary tuberculosis, found that in nearly every instance in which the urine was examined bacilli were found, and it is his belief that the examination of the urine is of greater importance than the examination of the sputum.

Caulk states that about 30 per cent of all surgical lesions of the kidney are tuberculous. He apparently agrees that the tubercle bacillus can be excreted by a normal kidney. He states that there can be tuberculous lesions in the kidney without any bacilli in the urine. He also cites a case in which bacilli were found in the bladder and right ureteral urine. The kidney was removed, although it looked perfectly normal. After a very careful search a small granular area was found at the base of one of the pyramids with no sign of caseation or cavity formation. In one section a small tuberculous focus was found and bacilli were demonstrated in the tissue. MacKenzie largely agrees with the findings above.

Calmette states that tubercle bacilli may be demonstrated in the urine under many circumstances, even when renal tuberculosis does not exist. He quotes Bertier as obtaining 33 per cent of positive guinea-pig inoculations in 24 cases of advanced febrile tuberculous cases, none of which was suspected of having renal tuberculosis. There apparently was no relationship between albuminuria and bacilluria as found by Kielleuthemer. Nobecourt, cited in the same text, examined 37 children with 4 positive

results. Of these 4, two had renal tuberculosis clinically, one had extensive pulmonary tuberculosis with cavitation, while the fourth had miliary tuberculosis with tuberculous meningitis. The urine of the patients suffering from nephritis of various types, with or without hematuria, gave constantly negative results. Leon Bernard is quoted as finding tubercle bacilli in the urine in 5 out of 42 adult cases of pulmonary tuberculosis without renal tuberculosis.

Braasch and Scholl state that excretory tubercle bacilluria must be considered. That this may be a factor in causing an erroneous diagnosis of renal tuberculosis remains yet to be proved. Their records do not show a single case in which this has occurred. They find that bilateral renal tuberculosis occurs more commonly than the usual cystoscopic data would lead them to believe. They also state that tuberculosis in the supposedly healthy kidney is probably a common cause of death within one or two years after nephrectomy.

Remlinger reports the result of inoculation of the urine of tuberculous guinea pigs into normal guinea pigs. Out of 24 cases he obtained 12 positive and 12 negative results. These 24 tuberculous guinea pigs all had miliary tuberculosis and none presented a single visible tuberculous lesion.

From the foregoing brief review of the literature it appears that two points may be studied with advantage in experimental animals. The first is to collect the entire urinary output of tuberculous animals in 24-hour quantities, or greater, over a period of several days or weeks. The sediment of these urines should necessarily be examined microscopically for pus and tubercle bacilli and should be inoculated into normal guinea pigs. The second point is that the kidneys from all of these animals in which the urine has been studied should be serially sectioned regardless of the gross appearance. Tubercle bacilli should be sought for in every kidney and all inflammatory lesions should be carefully studied microscopically, noting their origin and termination in relation to the kidney tissue.

We have carried out these two points on a series of 4 rabbits and 12 guinea pigs. Each series is necessarily small because of the labor involved in serial sections. In all, over 30,000 sections of kidneys have been examined carefully, many of them for tubercle bacilli.

The rabbits received two intravenous inoculations of bovine tubercle bacilli, Penn-State strain, 10 days apart. One-fourth of a 6-week-old culture on Dorset's egg medium was inoculated into the ear vein of each

rabbit. This strain of the bovine bacillus was not very virulent for rabbits and accordingly a rather large dose was used. The guinea pigs were all inoculated subcutaneously with approximately 20,000 human bacilli, H37, grown on glycerine-bouillon for 1 month.

Experiment 1. The rabbits were put in metabolism cages forty-eight hours before inoculation and two 24-hour specimens were collected in sterilized jars. The cages were all sterilized before the experiment began. All the urine from each specimen was centrifugated and about two-thirds of each sediment was inoculated subcutaneously into the groin of a healthy normal guinea pig. Smears of most of the sediments were examined microscopically for pus and tubercle bacilli.

From the 4 rabbits 73 specimens of urine were collected during a period of 45 days, and 73 guinea pigs were inoculated. Of these guinea pigs, 3 died of sepsis at the site of inoculation, 6 died of bronchopneumonia with no tubercle bacilli present, and the remaining 64 were killed within 60 to 100 days after inoculation. None of the guinea pigs showed any tuberculous lesions.

Sixty smears of the urine sediment were examined for tubercle bacilli and pus cells. An average of one hour was spent on each smear. Pus cells were found six times, and then they were rare. No typical tubercle bacilli were found. Large acid-fast bacilli were found eleven times, and then only a few in a smear.

The following are protocols of the 4 rabbits:

Rabbit 1: 0.5 cc. of heavy suspension of bovine tubercle bacilli intravenously on May 1 and May 11. Killed July 9, 1923. *Gross:* Tubercles were found at the site of inoculation. The lungs showed several tubercles scattered evenly throughout. No other evidence of tuberculosis was found. The kidneys showed a few small depressions on the surface, but appeared normal on section. Genitalia appeared normal. *Microscopic:* The lungs showed numerous small tubercles without caseation; bacilli found. Spleen, liver and adrenals showed no evidence of tuberculosis in the sections examined; kidneys, both sectioned serially, showed several small healed infarcts; two typical tubercles found, but no bacilli could be demonstrated; testes and seminal vesicles normal.

Rabbit 2: Inoculated and killed as above. *Gross:* There was tubercle formation at the site of inoculation. The lungs showed many small tubercles scattered evenly in all parts. The other organs all appeared normal. *Microscopic: Lungs:* Many tubercles; an occasional one showed a caseous centre. In places there were small areas of tuberculous bronchopneumonia. Bacilli easily found. *Spleen:* There were several small tubercles; bacilli found. *Liver:* A few small tubercles were present in the parenchyma and in the periportal spaces. Bacilli found. *Adrenals:* Negative. *Testicles:* Negative. *Kidneys:* Serial sections; no evidence of pathological changes; no bacilli found on examining 1,000 glomeruli.

Rabbit 3: Inoculated as above. Died 2 hours after second inoculation. *Gross:* There was tubercle formation at the site of inoculation. Adhesions obliterated the right pleural cavity. Both lungs showed extensive tuberculosis, some areas of caseation being present. The heart was dilated. The other organs were all congested. No evidence of tuberculosis was found in any of them on section. *Microscopic: Lungs:* Many tubercles, many of them showing considerable caseation. Bacilli easily found. *Spleen:* A few small tubercles, bacilli found with difficulty. *Liver:* A few small tubercles; no bacilli found. *Testes:* Normal. *Kidneys:* Serial sections; a few small healed infarcts with dilated convoluted tubules found. Three small tubercles were found. No bacilli could be demonstrated.

Rabbit 4: Inoculated as above. Killed July 9, 1923. *Gross: Lungs:* Many small tubercles were present in all portions of both lungs. All of the other organs appeared normal on

gross examination except for the unusual prominence of the malpighian corpuscles in the spleen. *Microscopic: Lungs:* Many tubercles; bacilli easily found. *Spleen:* Solitary and conglomerate tubercles; bacilli found. *Liver:* No tubercles found; organ appears normal. *Adrenals:* Normal. *Testes:* Normal. *Bladder:* Normal. *Kidneys:* Serial sections; a few healed infarcts were found; no evidence of tuberculosis; no bacilli found on examining 1,000 glomeruli.

While in two of these animals small lesions resembling tubercles were found, we could not demonstrate the bacillus and hence cannot claim that the lesions are tuberculous. We have no explanation to offer for the healed infarcts.

Experiment 2. The 12 guinea pigs used in this experiment were all being used in an experiment of a different nature in the laboratory. They were carefully watched, and when they became extremely ill were placed in metabolism cages and the urine collected. The specimens varied from 48 to 96-hour urinary outputs. They were treated in the same way as the specimens of the rabbit urine. They were all collected in the last week or ten days of the guinea pigs' life when the latter were overwhelmed with the infection. The length of life following the inoculation of the tubercle bacilli varied from 62 to 145 days. The reason for the great range in the length of life was that some of these animals were used in an experiment on immunization and hence lived longer than those given an inoculation of virulent bacilli and then left alone. Of these 12 guinea pigs 11 died of generalized miliary tuberculosis. One died of pneumonia, with very slight tuberculous lesions in the spleen, liver and inguinal lymph nodes.

From 9 of the 12 guinea pigs 16 urine specimens were collected. Of the 16 guinea pigs inoculated with these urine sediments, one died of pneumonia, 8 developed tuberculosis and 7 showed no tuberculosis when killed 3 months after inoculation.

Smears examined from the 16 urines showed typical tubercle bacilli 3 times, pus cells 9 times, and no pus cells 7 times.

Autopsy of these guinea pigs showed gross lesions, probably tuberculous, of the kidneys in 4 and no gross changes in 5. Examination of the kidneys microscopically by serial sections showed tuberculosis (lesions and bacilli found) in 7 and no tuberculosis in two.

If we add the 3 guinea pigs from which no urine was collected we have on gross examination 5 that have kidney lesions (probably tuberculous) and 7 that show no gross changes in the kidneys. On examining the kidneys from these animals by serial section, 8 showed lesions and bacilli, and 4 no lesions or bacilli.

Table 1 shows the result of this experiment.

From table 1 it will be seen that every animal in which the urine gave a positive inoculation proved to have renal tuberculosis. Two of the animals which had early tuberculous lesions in the renal cortex did not furnish positive inoculations, although they had extensive miliary tuberculosis. The two animals, which had no tuberculosis of the kidney microscopically, failed to show tubercle bacilli in their urine, although they also had extensive miliary tuberculosis. In other words, as far as this experiment goes we are led to believe that tubercle bacilli in the urine mean renal tuberculosis and that the absence of tubercle bacilli

TABLE 1

GUINEA PIG NUMBER	LENGTH OF LIFE	SMEAR URINE	GUINEA PIG INOCULATION	AUTOPSY							MICROSCOPIC						
				Lung	Liver	Spleen	Intestine	Adrenal	Kidney	Testis	Lung	Liver	Spleen	Intestine	Adrenal	Kidney	Testis
	days																
68	66	Neg.	Neg.	Slight	Ext.	Ext.	Ulcers	Neg.	Neg.	Neg.	Pos.	Pos.	Pos.	Pos.	Neg.	Neg.	Neg.
		Neg.	Neg.														
69	72	Pus	Neg.	Mod.	Ext.	Ext.		Neg.	Ext.	Neg.	Pos.	Pos.	Pos.		Pos.	Pos.	Neg.
		Pus and bacilli	Pos.														
		Pus	Pos.														
67	70	Neg.	Neg.	Mod.	Ext.	Ext.		Neg.	Neg.	Neg.	Pos.	Pos.	Pos.		Neg.	Pos., few lesions	Neg.
44	81	Neg.	Neg.	Slight	Ext.	Ext.	Neg.	Neg.	Neg.	Neg.	Pos.	Pos.	Pos.	Pos.	Neg.	Pos., few tubercles	Neg.
		Neg.	Neg.														
57	141	Pus and bacilli	Pos.	Ext.	Ext.	Ext.	Neg.	Neg.	Slight	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.
72	62	Pus	Pos.	Slight	Mod.	Ext.		Neg.	Neg.	Neg.	Pos.	Pos.	Pos.		Neg.	Pos.	Neg.
		Pus	Pos.														
60	122	Pus and bacilli	Pos.	Mod.	Ext.	Ext.	Neg.	Neg.	Mod.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos., few lesions	Pos.
62	110	Pus	Pos.	Ext.	Ext.	Ext.	Neg.	Neg.	Mod.	Neg.	Pos.	Pos.	Pos.	Neg., incomplete examination	Neg.	Pos.	
		Pus	Pos.														
69*x*	92	Neg.	Neg.	Slight	Ext.	Ext.	Neg.	Neg.	Neg.	Neg.	Pos.	Pos.	Pos.	Pos.	Neg.	Neg.	Neg.
		Neg.	Neg.														
10	120			Neg., pneumonia	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Pos.	Pos.		Neg.	Neg.	
35	145			Ext.	Mod.	Ext.	Neg.	Neg.	Neg.		Pos.	Pos.	Pos.	Pos.	Neg.	Neg.	
36*	131			Mod.	Ext.	Mod.	Neg.	Neg.	Mod.		Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	

Pos.: Positive; means lesion and bacilli found.
Slight: Small amount of pathological change.
Mod.: Moderate amount of pathological change.
Ext.: Extensive pathological changes.
Neg.: No evidence of pathological change.
* Died from ruptured spleen and abdominal hemorrhage. Intestinal lesions will be reported in a separate paper.

does not exclude tuberculous infection of the kidney. This implies, of course, that genital tuberculosis must be excluded. In this experiment two of the animals had genital tuberculosis and both of these had marked tuberculous lesions in the kidneys.

Of the 8 animals proving to have renal tuberculous lesions 7 had bilateral lesions. One, no. 67, had only three cortical tubercles in one kidney and no lesion in the other kidney.

The results of this experiment are at variance with the common belief of laboratory workers. Tuberculosis of the kidney has been believed to be extremely rare in guinea pigs. We have found it in 66 per cent microscopically, and in 40 per cent we suspected tuberculosis from the gross examination. A point of interest with regard to the kidneys was that they were not enlarged, and in only one instance was there any suggestion of pathological changes from external examination of the organs. In each of the animals both kidneys presented a similar appearance grossly.

A point of great importance is that, unless serial sections are made of both kidneys, small tuberculous lesions will unquestionably be overlooked. This proved to be true in guinea pigs 67, 44 and 72. Guinea pig 72 is of special interest because its urine proved to contain tubercle bacilli on two inoculations. In this animal the kidneys looked normal on gross inspection, both externally and on section. The serial sections of the left kidney showed one lesion near the middle of a pyramid, which had definite fibrosis and very little inflammatory exudate. After a long search one tubercle bacillus was found, phagocytosed by an endothelial leucocyte. This was the only lesion in the whole kidney and could hardly account for the presence of tubercle bacilli in the urine.

The right kidney of this animal showed again a single focus of infection in the outer part of one of the pyramids. This lesion happened to have been cut through on gross section of the kidney, and yet no evidence of its presence was seen. This lesion was very active, though small. Large numbers of tubercle bacilli, often in large clumps, were found in the inflammatory exudate in the tissues. On tracing this lesion through, a part was found where there was a definite erosion of the epithelium of the collecting tubules. From this point downward, polymorphonuclear and endothelial leucocytes were found in the lumina of these tubules, and many of these cells had tubercle bacilli in them. This lesion extended out toward the renal cortex as a small ray, but no tubercle bacilli could be demonstrated except in the active pyramidal portion.

Ext.: Extensive pathological changes.
Neg.: No evidence of pathological change.
* Died from ruptured spleen and abdominal hemorrhage. Intestinal lesions will be reported in a separate paper.

This evidently was a blood-borne infection, starting in a small vessel in the outer part of the pyramid. Had serial sections not been made, this lesion would have been entirely overlooked and we would have had a very good example of excretory bacilluria. A point of special interest is that a very small lesion may contain a tremendous number of tubercle bacilli. This small lesion had far more tubercle bacilli in it than most of the large lesions examined.

On microscopic examination of the right kidney of guinea pig 72 the pelvis over a portion of the pyramid showed a small area of erosion, with a small amount of inflammatory exudate in which tubercle bacilli were found. This small erosion was found to subtend the active lesion in the pyramid of the kidney. This finding would tend to support the belief of Caulk that if serial sections were made in human cases in which ulceration of the pelvis is found the majority would prove to have an initial lesion in the kidney substance.

As the tubercle bacillus is considered to pass through the wall of normal capillaries, it seemed of academic interest to search for the bacilli in the glomerular capillaries in these animals which had an overwhelming infection. Approximately 15,000 glomeruli were carefully studied, only the glomeruli not involved in a definite inflammatory process being considered. Bacilli were found within the capillaries in 10 instances, 6 times free and 4 times phagocytosed by the endothelium lining the capillary. No tubercle bacilli were found in the capsular spaces. In this connection it is well to bear in mind the pertinent remark of Krause that the tubercle bacillus, being nonmotile, must depend upon transportation the same as any foreign body introduced into the tissues.

TYPES OF LESIONS

While the tuberculous lesions in the guinea-pig kidneys tend to be of a more acute inflammatory character, because we are dealing with acute generalized miliary tuberculosis, still their distribution and general appearance are strikingly like those in the human kidney. We have here an excellent opportunity to study the character of these lesions by serial sections, a study which in the human kidney would be extremely laborious. In our study we have found that there are three types of lesion which, in the order of their frequency, are (1) cortical, (2) pyramidocortical, and (3) pyramidal.

The cortical lesion starts in a glomerulus, or in a vessel between the tubules in the cortex. It resembles early tubercles in the human subject, in that it is made up largely of endothelial leucocytes. There is little tendency to necrosis unless there are numerous bacilli. Increase of fibrous connective tissue with attempt at encapsulation is the rule. These are usually solitary discrete lesions, but in case the bacilli are not destroyed these lesions may spread to adjacent tissue by the phagocytosed bacilli being carried away from the parent lesion by the wandering of the leucocytes. These lesions show no connection with the medulla, and it is doubtful whether the bacilli reach the urine from these lesions unless they undergo necrosis and the walls of the tubules or lymphatics are broken down.

The pyramido-cortical lesions are always more or less fanshaped. They closely resemble infarcts. The lesion usually begins in the region of the arcuate arteries. As a general rule their medullary portions show very extensive necrosis with bacilli easily found. The collecting tubules subtending these lesions contain leucocytes and phagocytosed bacilli. The cortical part of the lesion may or may not show numerous tubercles. These tubercles may be solitary or conglomerate. Usually there is a distinct depression of the capsule over these lesions unless there are extensive cortical lesions when the capsule is bulging. Apparently, most of these lesions start in the vessels in the outer part of the medulla. Occasionally this type of lesion may be caused by a spread through the tubules and lymphatics from a necrosing cortical lesion to the medulla. In such a case tubules filled with leucocytes can be traced directly from the medulla to the cortical lesion. The pyramido-cortical lesion is the one in which there is the greatest destruction of kidney tissue which will eventually lead to cavity formation. There is a marked tendency for the lesions to spread in all directions through the necrosis and by bacilli being carried into adjacent normal tissue by the leucocytes. This type of lesion is probably the type of lesion seen in the human kidney when extensive destruction of the kidney substance takes place.

The pyramidal lesion is one which on serial section shows no connection with a cortical lesion. These lesions may arise either from a vessel infection in the pyramid or from a few tubercle bacilli being carried down the tubules or lymph channels from an ulcerating cortical lesion, which may later become quiescent. In this type of lesion there is again a marked tendency toward destruction of the kidney tissue. This lesion is rare. In the early lesions caused by hematogenous infection or lym-

phatic drainage of a cortical lesion, the inflammatory exudate is most marked in the tissue. The lesion arising as a result of drainage from a cortical lesion through the tubules shows the tubules filled with leucocytes and not so much inflammation in the tissue. At a later stage it is impossible to determine the exact origin of the lesion because of extensive necrosis.

In all cases in which an active pyramidal or pyramido-cortical lesion was present leucocytes and bacilli were found in the collecting tubules down to their opening into the pelvis of the kidney. Regardless of the size of these lesions there is drainage into the tubules because of necrosis of the tubular walls. Consequently one would expect to find pus and bacilli in the urine.

Hobbs feels that all tuberculous lesions, being hematogenous in origin, first localize in the cortical tissue, especially in the glomerular tufts, and that the other lesions which are seen are subsequently developed from these cortical foci. It is apparent that without serial sections a thorough study of the exact origin and distribution of the tuberculous lesions in the kidney is impossible. By the method used in this study it is felt that the knowledge gained is more exact. Our observations agree with Hobbs, in that the largest number of lesions does occur in the cortical tissue, but they do not agree in that these lesions are always the starting point for all lesions in the kidney. We feel that those lesions which have the characteristics of infarcts arise most commonly in the region of the arcuate artery. These lesions are the ones which bring about the most extensive destruction of the kidney tissue because of the more favorable conditions for the thriving of the tubercle bacillus. The cortical lesions lead generally to a much less destructive process and are far more favorable for encapsulation and limitation of the disease process.

The rôle of the lymphatics in the spread of tuberculosis within the kidney appears from our study to have been overemphasized. Undoubtedly the lymphatic drainage in the kidney, as in other organs, is toward the hilum and there would be no reverse flow unless there was marked blocking of the lymph. Crabtree believes that the smaller tubercles not involved in the larger lesions are due to a spread of the infection through the lymphatics of the kidney. From our study it appears that multiple foci of hematogenous infection are the rule and not the exception, and that the number of cortical lesions are more numerous than any other single type. To us it would appear that Crabtree was dealing with multiple primary hematogenous foci, rather than with a spread of the

disease through the lymphatics. One does not doubt that bacilli are carried through the lymphatics in the direction of the flow of the lymph current, but it is rather doubtful whether the bacilli are carried from one pole of the kidney to the other against lymph currents.

Another point of interest relative to the spread of tuberculosis to the kidney by the lymphatics was noted in two of the animals that had extensive peritoneal tuberculosis. Bacilli were very numerous in the exudate of both these animals. Tubercles were present in the peritoneal covering of the kidneys. Bacilli were present in considerable numbers in the exudate over the kidneys. Careful search was made, but in neither instance were we able to find tubercle bacilli within the capsule of the kidney. One of these animals, no. 68, showed no tuberculosis of either kidney. The other, no. 72, showed an active lesion in the pyramid in one kidney and a healing lesion in the other kidney. MacKenzie quotes Bromgersma as tracing tuberculous infection from the apex of the lung through the lymphatics along the aorta and through the diaphragm to the kidney. This explanation seems rather questionable to us when tubercle bacilli in such numbers lying right on the kidney fail to produce a renal tuberculosis.

The healing of tuberculosis of the kidney is believed by most authors never to occur. Caulk in his excellent article states that there has never been in the history of medical literature a single authentic case of spontaneous healing of a tuberculous kidney. Braasch and Schall in their recent article state that spontaneous recovery is exceedingly rare and that no pathologist has demonstrated a healed tuberculous lesion in the kidney. They have in recent years seen several cases in which spontaneous recovery evidently occurred. One realizes the difficulty of establishing the authenticity of a healed tuberculous lesion in the human kidney. Even in case one should find a scar in the kidney it would be impossible to be sure that the lesion was originally tuberculous. Undoubtedly the healing of tuberculous lesions, as usually seen, in the human being rarely if ever occurs because of the extensive destruction of the kidney tissue.

In our observations on renal tuberculosis in the guinea pig we have found no instance in our small series in which all of the lesions have healed. We were dealing in all instances with miliary tuberculosis and would consequently not expect such a condition. We have, however, found two lesions, which are either completely healed, or have gone very far toward complete healing by fibrosis. In one of these instances, guinea pig 72, after a long search in various parts of the lesion in the

left kidney a single tubercle bacillus was found. This was the only lesion in the entire kidney. In the other case, guinea pig 36, we were unable to find any bacilli in the fibrosed lesion even after a long search. We have here then two instances in which tuberculous lesions can heal in the kidney, as well as they can in other tissues of the body. In line with these observations are the interesting observations of Hobbs relative to the finding of fibrosed areas in the human kidney.

We realize that the observations here reported will be criticized in that they are not observations on human cases. The value of any observations on animal experimentation will depend on the understanding of the anatomy and physiology of the animals used and upon the interpretation of what is observed. As far as the anatomic structure of the guinea-pig kidney is concerned the only real difference noted in contrast to the human kidney is that in the former there is but one pyramid. The vascular supply and distribution are the same. The organic units apparently are the same. The physiology evidently is different in so far as the metabolism of the guinea pig and human being differ. The distribution of the tuberculous lesions in both are strikingly alike. In the guinea pig the lesions are of a more acute character because we are dealing with an overwhelming infection from the start. There is little hesitancy to apply deductions on immunological observations in animals, in a broad sense, to immunological problems in the human being. We feel that observations on tissue lesions and their distributions may, with as great justification, be applied to human lesions and their distribution, providing that the essential difference in organology and physiology be kept clearly in mind.

CONCLUSIONS

1. No evidence to support the excretion of tubercle bacilli from a normal kidney has been found.

2. Renal tuberculosis in the guinea pig is common; it occurred in 66 per cent of our series.

3. Bilateral renal tuberculosis is the rule; in 88 per cent of our series.

4. Cortical tuberculosis is the most common, but medullary lesions are the most destructive to the kidney tissue.

5. Serial sections are a necessity, to avoid overlooking tuberculous lesions in the kidney.

6. The size of the tuberculous lesion is no criterion as to the number of bacilli present.

7. Negative findings in the urine do not rule out renal tuberculosis.

8. Hematogenous infection is the rule; every case in our series. Usually there are multiple foci.

9. The tuberculous lesions in the guinea pig kidney are of three types: (1) cortical, (2) pyramido-cortical, and (3) pyramidal.

10. There is a striking resemblance between the tuberculous lesions in the guinea pig and human kidney.

11. Individual tuberculous lesions of the kidney may heal. Such a condition is probably rare, although undoubtedly more common than now believed. Further work will be done on this point.

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Tubercle bacilli were demonstrated in all lesions except in those of fig. 10

FIG. 1. Early microscopic lesion from right kidney of guinea pig 72. This was the only lesion in the entire kidney as revealed by serial sections. No lesions could be detected in the gross. Photograph shows entire transverse section of the lesion. Note the normal medullary kidney tissue surrounding the lesion. Note erosion of tubules in the lesion. This lesion was situated in the outer portion of the medulla. × 100.

FIG. 2. A higher power of the eroded tubules in fig. 1. Note the marked inflammatory reaction around the tubules and the polynuclear and endothelial leucocytes within the lumina. Tubercle bacilli were found in the cells within the lumina. × 360.

FIG. 3. High power of photograph of inflammatory exudate at edge of tubules shown in fig. 2. Note that the bacilli are phagocytosed by endothelial leucocytes (large cell above and to the left of centre) and by polymorphonuclear leucocytes (just below centre). Tubercle bacilli were very numerous in this lesion despite its small size. × 1000.

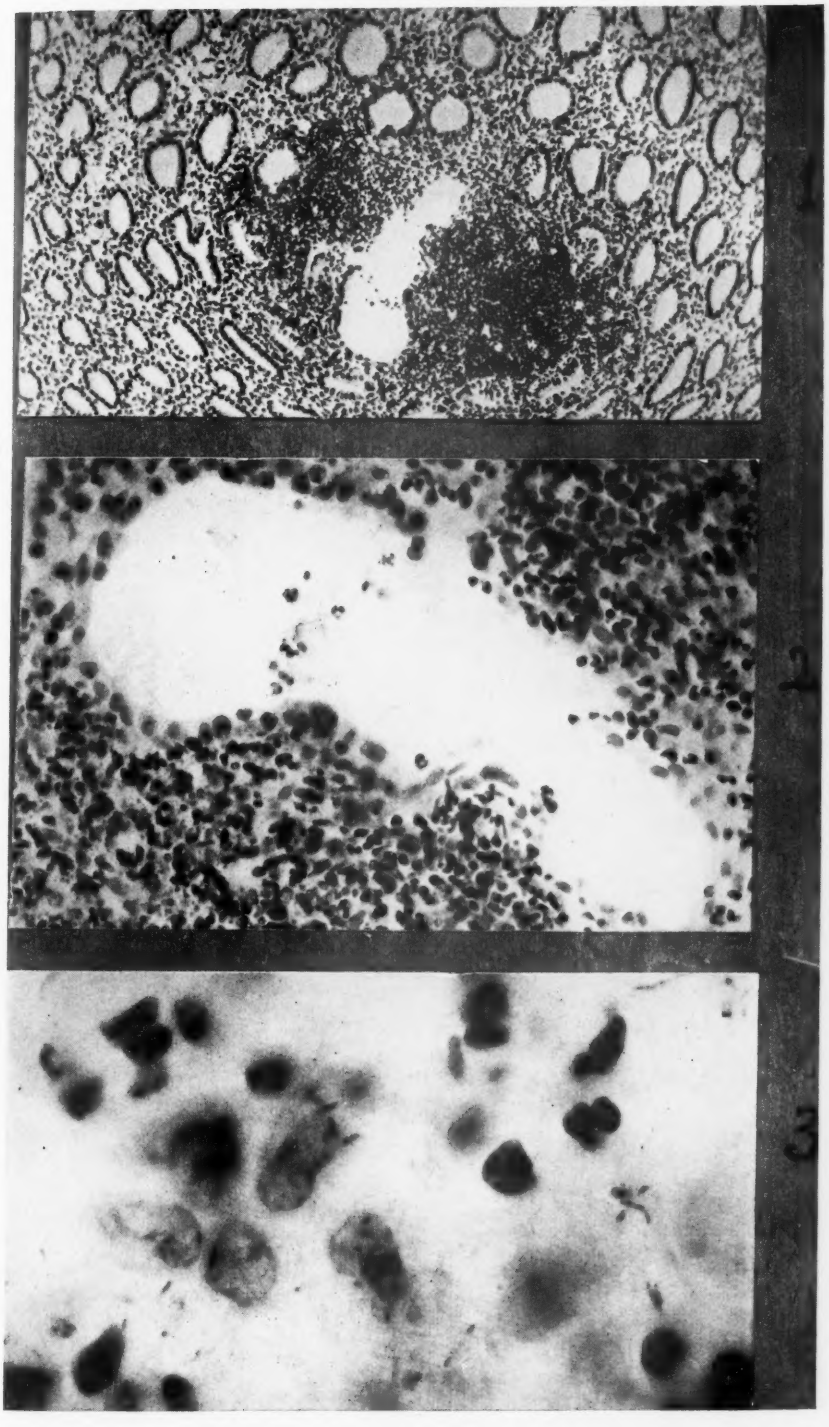
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FIG. 4. Photograph of extensive cortical lesion in the left kidney of guinea pig 69. This lesion had no connection with the medulla. Note the normal kidney tissue below the lesion. The renal capsule shows involvement at the upper part of picture. These cortical lesions are the most common and are usually multiple. × 20.

FIG. 5. A pyramidal lesion in the left kidney of guinea pig 69. This lesion was situated well down toward the tip of the medulla. It had no connection with the cortex. This type of lesion is rare. Note the extensive necrosis in the central portion of the lesion and the normal tissue surrounding the lesion. × 100.

FIG. 6. A pyramido-cortical lesion in the right kidney of guinea pig 57. The lesion started as an extensive cortical lesion which drained through the lymphatics and tubules into the medulla. Note the following points: The inflammation connecting the cortical and medullary portions of the lesion; the tubules in both portions filled with inflammatory reaction. This type of lesion is less common than the type shown in figs. 7 and 8. × 40.

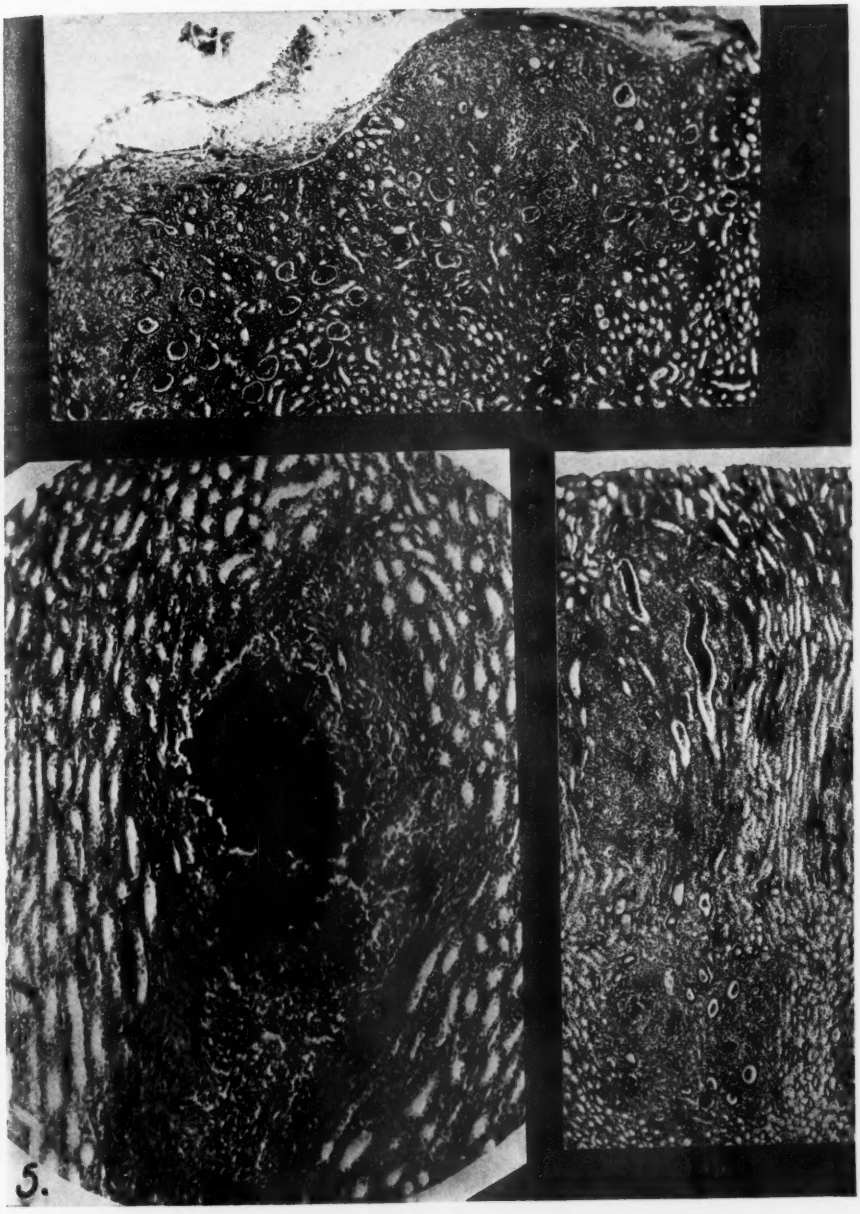
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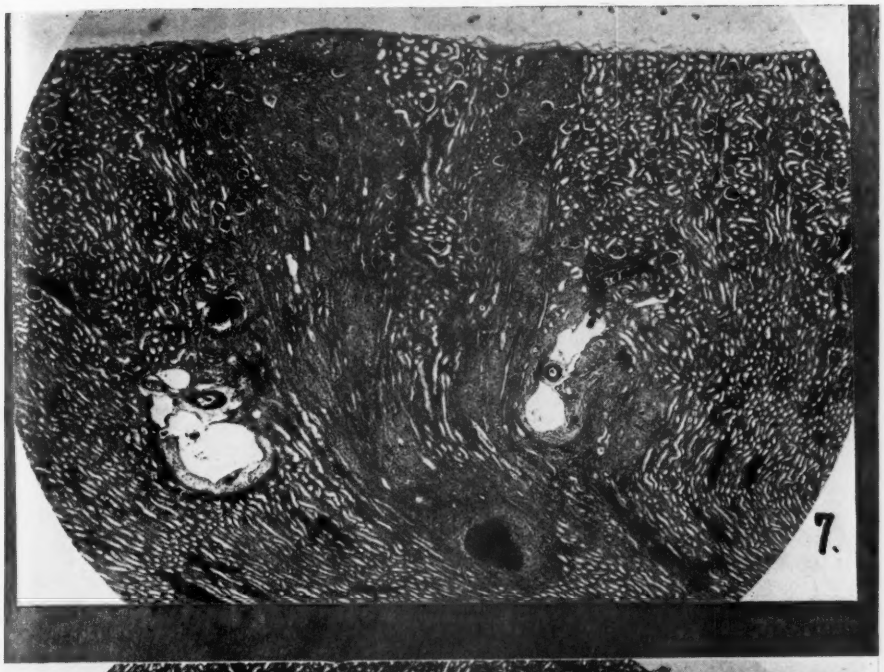
FIG. 7. A pyramido-cortical lesion in the right kidney of guinea pig 69. Section shows two lesions. Note the wedge-shaped nature of the larger lesion and the direct continuance of the lesion from the outer medulla to the cortex. There is extensive necrosis in the medullary portion. This lesion strongly resembles an infectious infarct. This type of lesion is next in frequency to the cortical lesion. It is the most destructive type of lesion. × 20.

FIG. 8. A pyramido-cortical lesion in the left kidney of guinea pig 69. Note the extensive necrosis of the medullary portion of the lesion. The lesion extends from here out to the cortex, but there are very few tubercles and very slight inflammatory reaction. The photograph shows a solitary tubercle near the capsule and one about half way out from the pyramidal lesion. The lesion is the same type as shown in fig. 7, except that in this lesion there is very slight involvement beyond the medulla. × 20.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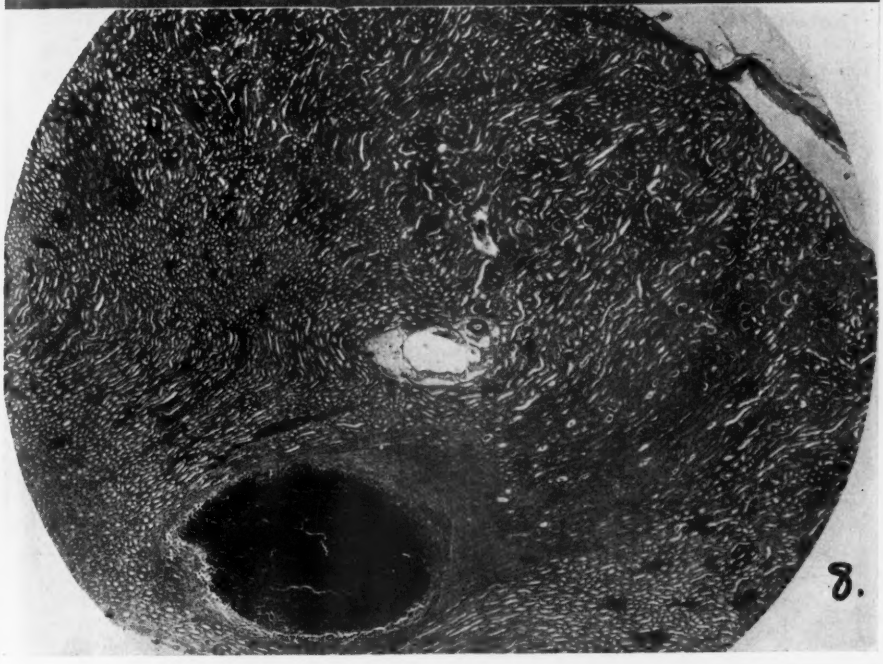
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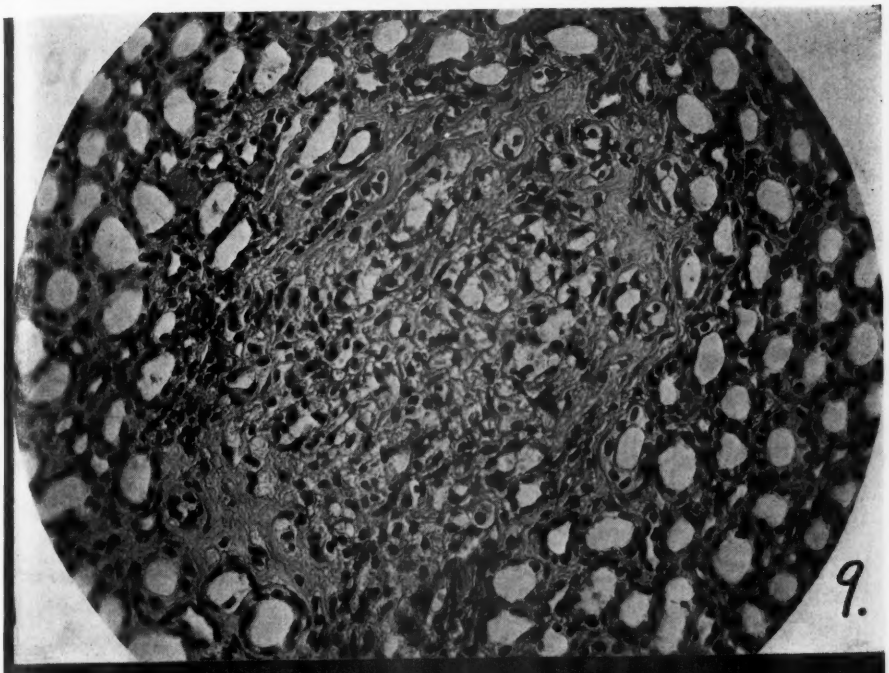
FIG. 9. Section of a lesion in the outer portion of the medulla in the left kidney of guinea pig 72. This lesion was of the pyramido-cortical type. No active lesion was present in any portion. Note the extreme fibrosis. After prolonged search one tubercle bacillus was found in the lesion. Section shows the least fibrosis of any portion of the lesion. × 250.

FIG. 10. A fibrosed lesion in the right kidney of guinea pig 36. There were active acute lesions in the other parts of this same kidney. This lesion is of the pyramido-cortical type. No tubercle bacilli could be found in sections of the lesion although prolonged search was made. Note the extensive fibrosis, the foreign-body giant cells and the moderate lymphocytic infiltration in the periphery of the lesion. Note also the normal tissue around the lesion. × 100.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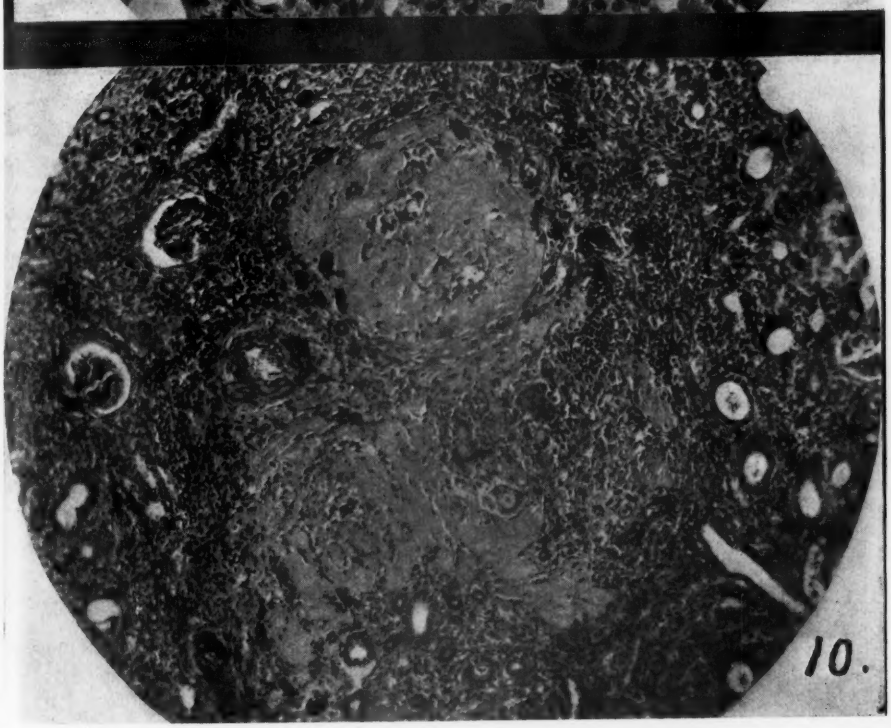
10.

A STUDY OF THE PRESENCE OF TUBERCLE BACILLI IN THE BILE AND OF THE TUBERCULOUS LESIONS OF THE LIVER IN EXPERIMENTAL ANIMALS[1]

K. T. SASANO AND E. M. MEDLAR

The presence of tubercle bacilli in the bile of some human cases dying from tuberculosis and of a considerable percentage of experimental animals dying from generalized miliary tuberculosis has been established. This fact has led recently to the advocacy of the examination of the bile, obtained by the duodenal tube, for tubercle bacilli in those tuberculous cases in which it has been impossible to demonstrate the bacilli in the sputum.

Fraenkel and Krause (1) in 1899 were the first to demonstrate tubercle bacilli in the bile. The bile was obtained at autopsy on tuberculous patients. These cases showed no evidence of hepatic tuberculosis on gross examination. Five out of eleven biles were positive.

Calmette (4) and his school have attracted most attention to the presence of tubercle bacilli in the bile. The following quotations are taken from the American translation of Calmette's book on tuberculosis:

> The fact is to-day well established that many bacteria introduced into the circulation may be eliminated through the intestines.
>
> By means of another technique I proved, collaborating with C. Guérin, that the tubercle bacillus can likewise be eliminated by the bile ducts. We injected, into the marginal ear vein of a series of rabbits, one centigramme of finely suspended bovine bacilli from a six-week-old culture on glycerine potato. The animals were killed by cutting the throat 24, 48 hours, 3, 4, 5, 6, and 7 days, respectively, after inoculation. The body was immediately opened and, with every care taken not to touch the surface of the liver, the contents of the gall-bladder were aspirated with a pipette and centrifugated. The sediment from the centrifugation was diluted with 2 cc. of physiological salt solution and inoculated in a dose of 0.5 cc. into four guinea pigs. The same procedure was carried through with each rabbit. All the guinea pigs which received bile from the rabbits sacrificed 24 and 48 hours and 5 and 6 days after infection, remained free from infection, while of the four which received the bile from the rabbit of the third day, two were tuberculous, as was one of the four which received the bile of the rabbit on the fourth day and three of those which received bile of the rabbit killed on the seventh day.

[1] From the John Rogers Hegeman Memorial Laboratory, Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York.

It is evident therefore that a part of the bacilli introduced into the blood-stream may be eliminated through the liver and evacuated with the bile through the intestine.

We performed another experiment which was still more conclusive. In two heifers we made a permanent biliary fistula which enabled us to draw off from the gall-bladder at will, with the aid of a pipette, the quantity of bile necessary for test inoculations. One of the heifers received three milligrammes of virulent bovine bacilli into the jugular vein. Each day before and after the injection, a small quantity of bile was withdrawn from the gall-bladder and 0.5 cc. injected into each of four guinea pigs. Of the total of 109 animals, 15 became tuberculous, all of which had received bile collected more than 19 days after the inoculation of the heifer. This animal died of acute miliary tuberculosis on the 28th day.

When one considers the minute quantity of bile injected (0.5 cc.) and the enormous volume (about 2 litres) of this fluid excreted by the heifer in 24 hours, one is forced to conclude that the number of bacilli evacuated through the bile passages of this animal is considerable.

One must therefore conclude that the bacilli are frequently transported to the liver in the circulating blood and eliminated through the bile.

Remlinger (3) reports that out of the biles obtained from 24 tuberculous guinea pigs 18 proved to contain tubercle bacilli and 6 were noninfectious. No record of careful examination of the livers in these cases was reported.

Joest and Emshoff, as quoted by Calmette, found that in 25 per cent of 57 cattle and swine having generalized tuberculosis the bile contained tubercle bacilli. Rabinowitsch, quoted by the same author, found that 8 biles from 17 tuberculous cattle contained tubercle bacilli. Only one of these animals had gross tuberculosis of the liver.

Corper, Simmons and Freed (9) examined the bile from 26 human cases of tuberculosis at autopsy. In six instances the bile contained tubercle bacilli, as shown by guinea-pig inoculation. Of these six positive biles four were obtained from 18 far advanced cases. One of these had generalized miliary tuberculosis. One of the positive biles was obtained from a moderately advanced case of tuberculosis and the sixth positive bile was obtained from a tuberculous patient who died from an aortic aneurysm. These authors also quote the work of Rabinowitsch (2) who obtained eleven positive biles out of sixteen far-advanced cases of tuberculosis. One positive bile in her series was obtained from a case in which the only tuberculosis found was in the mesenteric lymph nodes. Of these twelve positive cases eight had tuberculous enteritis. Most of the livers were reported as negative.

Recently Freed and Black (5) and Libert (6) have reported the finding of tubercle bacilli, obtained from the fractional biles by the Lyon-Meltzer technique, in cases in which they were unable to demonstrate the bacilli in the sputum, gastric or duodenal contents. They stress the importance

of this technique in establishing the presence of tuberculosis in those cases in which a positive diagnosis has not been possible otherwise.

The work here presented was undertaken to ascertain the relation of the tubercle bacilli in the bile to the condition in the liver; that is, to try to determine whether tubercle bacilli could be found in the bile when there was no tuberculous lesion in the liver. A total of 26 carefully selected guinea pigs have been studied during the past two years. All but one of these animals were infected with pure cultures of H37. One animal, no. 34, was inoculated with urine sediment. Twenty-one were subcutaneously inoculated in the groin. Seven of these animals had massive gross tuberculosis of the liver, five had slight gross tuberculosis of the liver, eight showed no gross tuberculosis of the liver and one showed gross tuberculosis of inguinal lymph nodes only. Six animals were infected by inhalation; of these, five showed only slight tuberculosis of the lungs and peribronchial lymph nodes and one showed tuberculosis of the spleen, lungs and lymph nodes, with no gross evidence of liver involvement. Five animals were infected intratracheally; all of these showed slight tuberculosis of the lungs and peribronchial lymph nodes, but no gross involvement of any other organs. Two animals were fed bacilli and two were given intravenous inoculation. These four animals were killed before gross lesions could possibly develop.

All of the biles were inoculated subcutaneously in the groin. As much bile as possible was obtained aseptically either at autopsy or by surgical procedure.

The livers which showed no gross involvement were fixed *in toto*. The other livers were sectioned and portions fixed for microscopic study.

The result of the bile inoculations are shown in table 1. In this table the animals are grouped according to the extent of tuberculous involvement of the liver. Table 1 shows that in every guinea pig examined in which there was massive hepatic tuberculosis the bile contained tubercle bacilli. In five cases having slight hepatic tuberculosis on gross examination tubercle bacilli were present in the bile in two. In 24 cases which showed no definite gross evidence of hepatic tuberculosis the bile was found to contain tubercle bacilli three times.

HISTOLOGICAL STUDY

Since it has been unquestionably established that bile taken aseptically from the gall-bladder does at times contain tubercle bacilli, it

TABLE 1

Summary in table form

NUMBER OF ANIMAL EXAMINED	ANATOMIC DISTRIBUTION OF TUBERCULOSIS	TUBERCLE BACILLI IN BILE
1	Massive infection of liver with involvement of other organs	+
2	Massive infection of liver with involvement of other organs	+
6	Massive infection of liver with involvement of other organs	+
10	Massive infection of liver with involvement of other organs	+
11	Massive infection of liver with involvement of other organs	+
13	Massive infection of liver with involvement of other organs	+
12	Slight infection of liver with involvement of other organs	0
14	Slight infection of liver with involvement of other organs	0
15	Slight infection of liver with involvement of other organs	+
16	Slight infection of liver with involvement of other organs	+
20	Slight infection of liver with involvement of other organs	0
17	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
18	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
19	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
25	Lungs, spleen and lymph nodes with no visible hepatic lesions	+
33	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
34	Lungs, spleen and lymph nodes with no visible hepatic lesions	+
35	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
36	Lungs, spleen and lymph nodes with no visible hepatic lesions	0
5	Thoracic cavity only. Early pulmonary tuberculosis	0
23	Thoracic cavity only. Early pulmonary tuberculosis	0
24	Thoracic cavity only. Early pulmonary tuberculosis	0
26	Thoracic cavity only. Early pulmonary tuberculosis	0
27	Thoracic cavity only. Early pulmonary tuberculosis	0
28	Thoracic cavity only. Early pulmonary tuberculosis	0
29	Thoracic cavity only. Early pulmonary tuberculosis	0
30	Thoracic cavity only. Early pulmonary tuberculosis	0
31	Thoracic cavity only. Early pulmonary tuberculosis	0
32	Thoracic cavity only. Early pulmonary tuberculosis	0
21	Slight tuberculous infection with nontuberculous peritonitis	+
22	Left inguinal glands only	0
3	Tubercle bacilli ingested; 36 hours, no tubercle	0
4	Tubercle bacilli ingested; 72 hours, no tubercle	0
7	Tubercle bacilli injected; 24 hours, no tubercle	0
8	Tubercle bacilli injected; 72 hours, no tubercle	0

seemed to us that, before assuming the possibility of the excretion of tubercle bacilli by the liver without there being tuberculous lesions in that organ, it would be necessary to make a very careful microscopic study of those livers which showed tubercle bacilli in the bile. Our recent reports on renal and intestinal tuberculosis have shown the importance of serial sections in the study of the early tuberculous lesions in an organ. We have employed the same technique in this study.

The livers, noted in table 1 as having gross tuberculosis, were proved microscopically by finding the bacilli. Of the three livers which showed no gross tuberculosis and yet had positive bile, one (case 25) was lost, one (case 34) was serially sectioned and the third (case 21) was sectioned sufficiently to enable a positive diagnosis of tuberculosis. In other words, eleven of the livers which had tubercle bacilli in the bile all proved to have tuberculous lesions microscopically and the twelfth was not microscopically examined. The microscopic findings obtained by a careful systematic study of the serial sections from case 34 are fully given below because of the explanation they offer for the interpretation of the presence of tubercle bacilli in the gall-bladder. This animal was subcutaneously inoculated in the groin with urine sediment from a case of suspected renal tuberculosis and was killed on the forty-second day.

One of the first things which was noted in the study of the serially sectioned liver was the uniform involvement of the periportal system throughout the organ. This involvement consisted of inflammatory exudate of endothelial leucocytes, polymorphonuclear leucocytes and lymphocytes in corresponding proportions. Giant cells were rarely found in these areas. The most outstanding feature was the slight to very extensive accumulation of the inflammatory cells within the lumina of the various branches of the portal vein, which in many instances completely occluded the lumen of the vessel. The lymph channels could often be easily picked out because they were dilated and packed with leucocytes of the above types. The bile ducts, which are an integral part of the periportal spaces, rarely showed involvement in this early process, although they were completely surrounded with this inflammatory exudate, often showing compression of the lumen. At times it was necessary to examine these areas with high power, to establish the presence of bile ducts in the area, so dense was the cellular exudate. The hepatic artery branches usually showed no involvement such as the branches of portal vein.

The most surprising feature was the contrast between this extensive involvement of the periportal tissue and the scarcity of lesions in the liver parenchyma. The parenchymal tissue immediately adjacent to the periportal tissue was usually involved, sometimes to quite an extent. Beyond this involvement lesions were hard to find. As one proceeded from the periportal tissues toward the central vein the lesions became fewer. In the whole liver only five lesions were found adjacent to or involving a central vein. The sublobular veins were always free.

The earliest parenchymal lesion consisted of small accumulations of cells, chiefly polymorphonuclear leucocytes, within the sinusoids. Later the endothelial leucocyte predominated and typical tubercles with giant cells were formed. These lesions were always small, contained few bacilli, and very rarely showed any evidence of necrosis. They were more typical tuberculous lesions, histologically, than the periportal lesions and were too small ever to be found macroscopically.

One interesting lesion was found in which the tuberculous process extended from the periportal tissue directly across a liver lobule and involved the central vein.

Occasionally one finds in this early hepatic tuberculosis small areas of necrosis of the parenchyma. This varied from a small area adjacent to the periportal tissue to the complete involvement of one or more lobules. The large proportion of these lesions showed no inflammatory reaction and no tubercle bacilli could be found. In the livers showing a more advanced tuberculosis infarcts are common. It seems probable that these small areas are early infarcts, caused by the extensive plugging of the portal-vein system because of the accumulation of cells within their lumina.

Three or four small infarcts were also found in the periportal tissue in the serially sectioned liver. These infarcts were undoubtedly due to the complete plugging of both the portal vein and hepatic artery supplying the region involved. In these infarcts often all the tissue, including bile ducts and blood vessels, was necrosed. Tubercle bacilli could be found in these areas; but it is probable that they were present in an inflammatory exudate in the tissue before infarction took place. This type of lesion is undoubtedly the forerunner of the large bile-stained lesions which are commonly seen in advanced tuberculosis of the guinea-pig liver.

In this early stage of tuberculosis it was very rare to see any evidence of caseation in the periportal tissues. One lesion was found in which

caseation was present. The area of caseation involved the bile duct directly. Tubercle bacilli are numerous in this type of lesion, there being as high as two dozen in a single microscopic field.

In studying the distribution of the lesions within the periportal system it was found that the greatest amount of lesion was present in the periportal spaces of medium size. The smallest periportal spaces, which consisted of a thin-walled vein, one or more small bile ducts and two or three small lymph channels, rarely showed more lesion than a dilatation of the lymph ducts due to accumulation of cells within them. This apparently is the earliest periportal lesion. The major portion of these terminal periportal spaces showed no lesions. When one reached that portion of the periportal system where the blood vessels, lymph spaces and bile ducts were large, inflammatory reaction again was slight. In these areas one commonly found a moderate number of cells in the lymph. Between these two extremes there was extensive inflammatory exudate.

A careful study of the bile ducts in their relation to the inflammation was made. The evidence was conclusive that the inflammation was due to tubercle bacilli outside of the ducts. The great majority of the ducts were uninvolved. Where the exudate was marked one often found it encroaching upon the bile-duct epithelium, the leucocytes being between these cells and even in the lumen. Leucocytes were found within the lumina of the ducts in infarcted and caseous areas. In three instances bile ducts of medium size were found with the epithelium in one portion destroyed and the periductal inflammatory reaction extending directly into the lumen. In other words the tuberculous process had caused a small ulceration of the bile duct. Leucocytes were rarely found in the larger bile ducts. It is probable that the leucocytes which do get into the bile ducts are in time dissolved and that this accounts for their scarcity in the large ducts. We have proved expêrimentally that bile *in vitro* does dissolve leucocytes.

It has long been contended that tuberculosis in the guinea pig differs radically from human tuberculosis, especially in that there is far more tuberculosis of the spleen and liver than in human cases and far less in the lungs.

If the *modus operandi* of tuberculosis in human and guinea-pig livers is essentially different, then the attempt to claim that the human liver excretes tubercle bacilli because it has been demonstrated that tubercle bacilli are excreted in the bile of experimental animals is futile. If the lesions are essentially the same then the observations made on experi-

mental animals may justly be applied to a similar process in man. Because of this apparent difference there has been great hesitancy to concede that the tuberculous process in experimental animals is comparable to the tuberculous process in man.

In studying the anatomic and histological structure of the guinea-pig liver one finds that in the main features they agree with the human liver. The blood supply, lobular structure, contents of the periportal and sublobular spaces, the lymphatic system and the biliary system are in the guinea pig analogous to the human. Therefore, in so far as the anatomic features are concerned there is no apparent reason why the tuberculous process might not be analogous.

Tuberculosis of the liver is concisely described by Mallory (7) and by Aschoff (8). The most common type of lesion is the small tubercle in miliary tuberculosis. These lesions are most common in the parenchymal tissue adjacent to the periportal spaces. They usually have giant cells, remain small in size and tend to become encapsulated. A rarer type is that in which the periportal tissue becomes extensively involved. In this type giant cells are rare. Necrosis may lead to erosion of the bile ducts and, consequently, a bile-staining of the tissues. This form may lead to a biliary sclerosis and an extensive chronic tuberculosis. This process develops when considerable numbers of tubercle bacilli are carried to the liver through the blood-stream. It is called the bile-duct type of tuberculosis.

A third type of human hepatic tuberculosis which is very rare is the solitary tubercle. Aschoff states that this solitary tubercle may under favorable circumstances reach the size of a man's fist.

In our study of the early tuberculous lesion in the guinea-pig liver we find that we are dealing with the bile-duct type of tuberculosis which appears second in frequency in the human liver. The distribution of the lesions, the type of inflammatory exudate, the bile-stained areas in the older process and the sclerosis, all correspond to the description Mallory gives of bile-duct tuberculosis in the human liver. The presence of infarcts in the guinea-pig liver is the only point of difference. This difference is probably due to the fact that tubercle bacilli are fed more constantly and in greater numbers to the guinea-pig liver, and hence this leads to a more acute and extensive inflammatory reaction which brings about the plugging of the vessel lumina with leucocytes.

We have also noted in our description above that when there are miliary tubercles in the guinea-pig liver they are invariably in the par-

enchymal tissue adjacent to the periportal space, that they tend to remain small and are of a more typical tubercle structure than the lesions in the periportal spaces. This again agrees with the miliary tuberculous process in the human liver when the tubercle bacilli reaching the liver are few in number.

In two guinea pigs, which had been partially immunized against strain H37, we have recently seen solitary tubercles in the liver, each tubercle being about the size of a pea. These were surrounded by a dense wall of fibrous tissue and had caseous centres. This corresponds to the solitary tubercle in the human liver.

The guinea-pig as well as the human liver is an excellent filter. Very few tubercle bacilli get far from the periportal space, if one may judge at all from the presence or absence of inflammatory reaction. At least it is far more difficult to find tubercle bacilli in the parenchymal lesions than it is in the periportal lesions.

It would seem then that the tuberculous process in the guinea-pig liver is analogous to that in the human liver. The main reason for the apparent difference, as far as gross pathological changes are concerned, lies in the fact that the human liver rarely has considerable numbers of tubercle bacilli carried to it, while in the guinea pig this is a common occurence because of the overwhelming miliary infection. When the human and guinea-pig livers are put under the same conditions of infection it is apparent that the result will probably be the same.

DISCUSSION

The main purpose of this paper was to study the possibility of the excretion by the liver, in the course of its normal physiological function, of a nonmotile particulate body such as the tubercle bacillus. The presence of tubercle bacilli in the bile under certain conditions is unquestioned. How the tubercle bacilli arrived in the bile is, however, open to dispute.

Calmette and his school apparently believe that one of the functions of the kidney, intestines, and liver is to excrete pathogenic bacteria, once they have entered the circulation, without any lesion being produced in the organ during the transit of the bacteria. Corper and his colleagues quote the work of Drinker in which he demonstrated the presence of insoluble manganese compounds in the bile, following their intravascular injection, as offering an explanation of the way in which tubercle bacilli

are excreted from the liver. These manganese particles were much smaller than the tubercle bacillus. These observations have led several investigators to attempt to demonstrate tubercle bacilli in fractional bile as obtained by the Lyon-Meltzer method in cases of suspected pulmonary tuberculosis in which it has been impossible to demonstrate the bacilli in the sputum.

The recent work of Boardman (11) throws considerable doubt on the value of any deductions relative to the origin of the bacteria present in the fractional bile obtained by the Lyon-Meltzer method. He made a careful study of the bacterial flora of the pharynx, fasting stomach contents and fasting duodenal contents in 56 cases and found that the bacterial flora of bile *b* differed from all of these in only 5 per cent and of bile *c* in only 8 per cent. His conclusion is as follows: "With these findings, it seemed apparent to us that no reliance could be placed on the bacteriological findings in the various bile samples and that even with the most painstaking technique, including the study of the mouth and stomach flora, the procedure is bacteriologically so fundamentally faulty, that its use in the routine clinical study of the 'duodenal biliary zone' is apt to lead to more incorrect than correct conclusions."

It is rather hard to understand the work of Drinker except on the basis of diffusibility of the manganese compounds. Nagao (10) in his careful study of the fate of india-ink particles, intravenously injected, states that "the granules being nondiffusible, are not discharged from the cells by any excretory process, but are liberated only on disintegration of the cell." It seems to us that the tubercle bacillus can be more aptly considered as belonging to a group of nondiffusible substances, and hence its excretion would be all the more difficult.

In the experiments recorded by Calmette he was unable to demonstrate tubercle bacilli in the bile before 72 hours after fairly heavy intravenous inoculation of rabbits. In calves this appearance was delayed to the nineteenth day after inoculation. This delay of appearance of tubercle bacilli in the bile following intravenous injection has also been established in our experiments. Such delays are not noted in the case of chemical substances that are excreted by the liver.

As shown by our experiments and by others, the bile does not constantly contain tubercle bacilli, even when there is considerable tuberculosis present in the body. In these cases the liver may be involved. It is possible that in those cases in which the liver is involved the collection of the entire bile output of 24 hours or longer might show tubercle bacilli

present. In our renal tuberculosis work we have shown that there may be tuberculosis in the kidney without tubercle bacilli being in the urine. This probably also holds for the liver. The normal excretory systems of both these organs are closed, as far as is known, to everything but diffusible substances.

From our study of the serial sections of the tuberculous liver, in the stage in which enlargement was not apparent and in which gross diagnosis was not possible, it would appear that a far more logical explanation of the presence of tubercle bacilli in the bile would be that there is present in the liver a caseous tubercle or an infarct, which leads to necrosis of the bile-duct epithelium and thus an opening for the tubercle bacillus into the biliary system. In other words lesion and necrosis in the liver must necessarily precede the appearance of tubercle bacilli in the bile. We believe it illogical to expect tubercle bacilli in the bile without ulcerative tuberculous lesions in the liver and all the histological observations we have made support this belief.

If tubercle bacilli are present in bile obtained by the Lyon-Meltzer technique one must conclude that they were either ingested or that there is an ulcerative tuberculous lesion in the liver. If the latter be true tuberculosis of the liver is much more common in the human case than at present suspected.

CONCLUSIONS

1. Tubercle bacilli commonly occur in the bile in cases in which there is gross hepatic tuberculosis in the guinea pig.

2. The hepatic tuberculosis of the nonimmunized guinea pig infected with virulent bacilli is of the bile-duct type. It corresponds very closely to the same type in the human liver.

3. Tuberculosis of the liver was found in every case in which tubercle bacilli were demonstrated in the bile. Tubercle bacilli in the bile means tuberculosis of the liver.

4. Evidence is presented in favor of an ulcerative tuberculous lesion in the biliary system as a precursor to the appearance of the bacilli in the bile.

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Tubercle bacilli were demonstrated in all lesions except the first and last. All the lesions photographed were taken from the serially sectioned liver of guinea pig 34

FIG. 1. Early tuberculous lesion in small periportal space cut longitudinally. Blood vessel lies above and bile duct below the lymph duct which is dilated with white blood cells. × 100.

FIG. 2. Cross-section of periportal space showing accumulation of white blood cells in a branch of the portal vein, adjacent to a tuberculous lesion below and to the left, and another above and to the right. Note several lymph ducts free from inflammatory reaction. × 100.

FIG. 3. Longitudinal section of periportal space showing in the central portion a branching of the portal vein, which is filled with white blood cells. Note the extensive inflammatory exudate in the periportal tissues without giant cell or tubercle formation. × 50.

FIG. 4. Cross-section of periportal space showing a small infarct. A bile duct lies in the infarcted area a little to the right of the centre of the picture and shows necrosis of its epithelium with several leucocytes, polymorphonuclear and endothelial, within the lumen. A branch of the portal vein, occluded with leucocytes, lies to the left of the infarcted area. × 100.

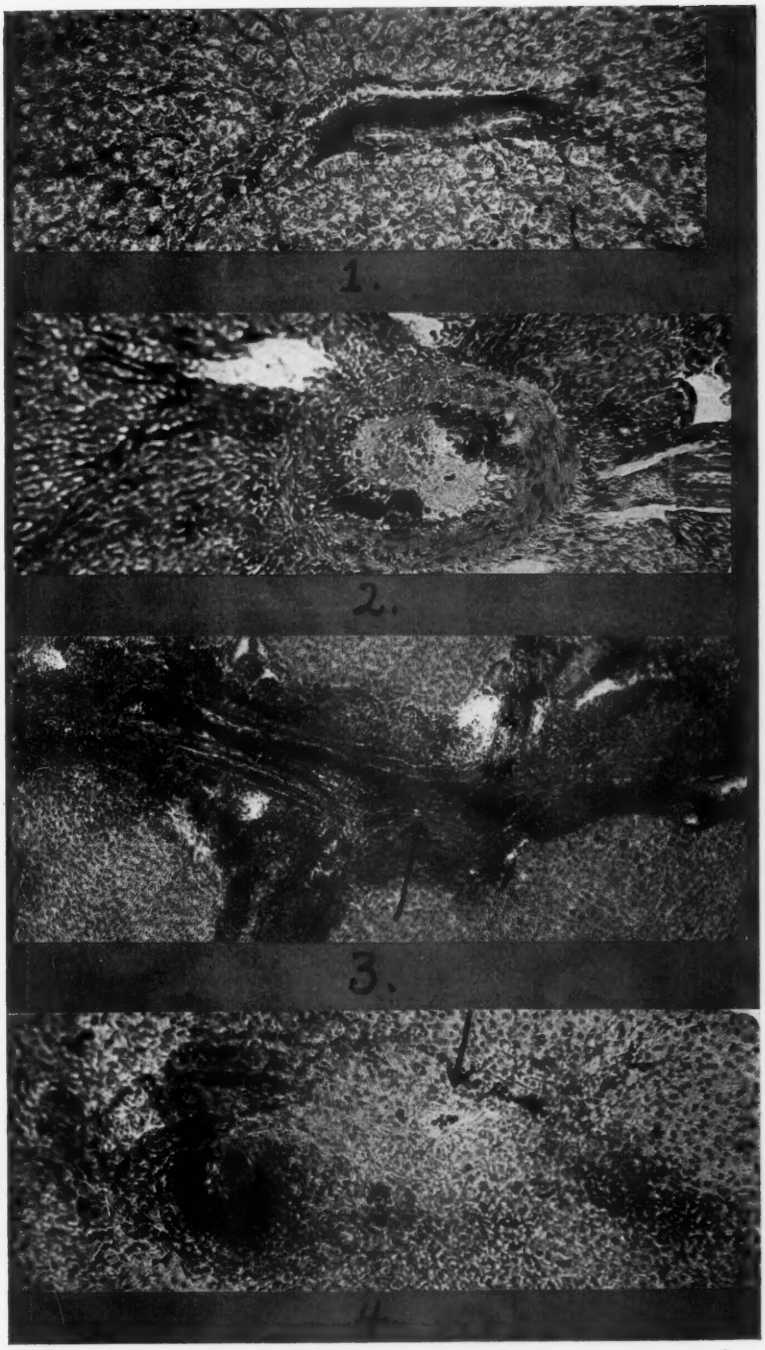
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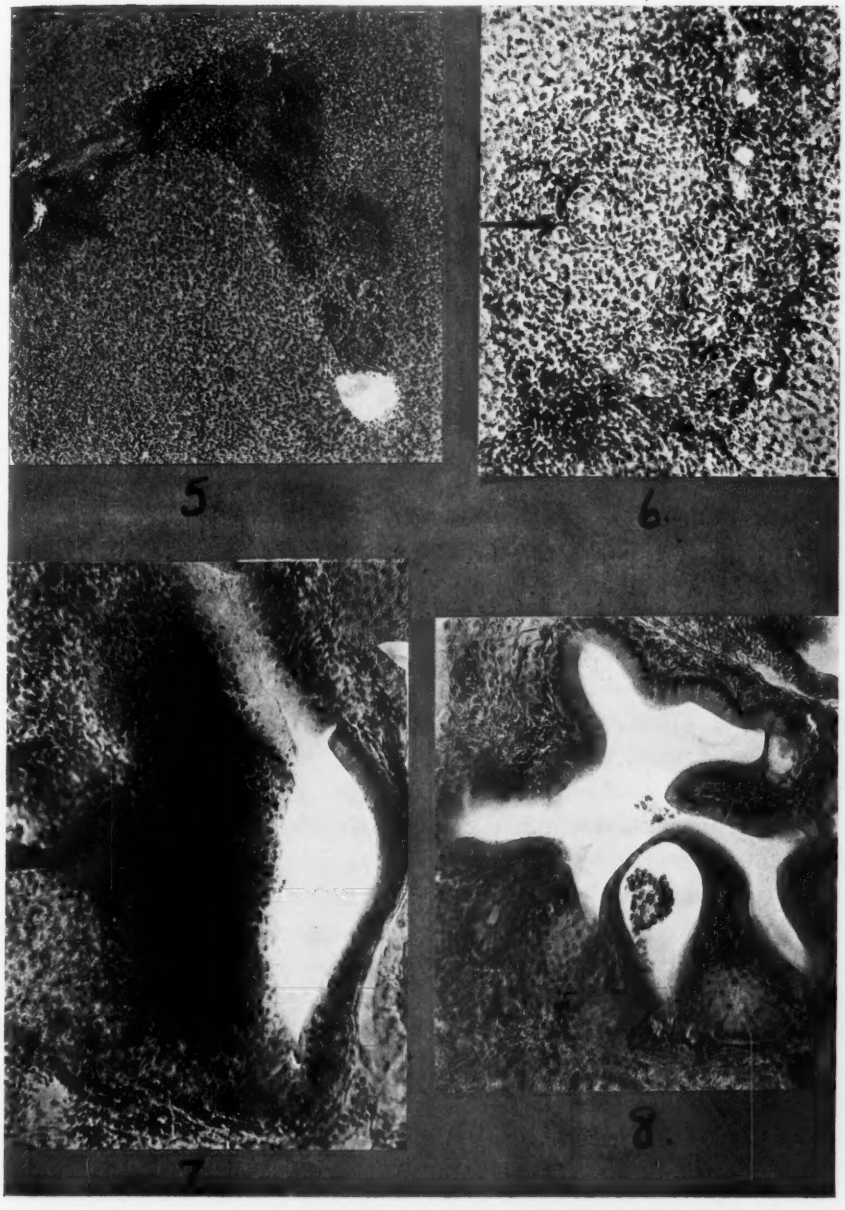
FIG. 5. A tuberculous lesion involving a periportal space and a liver lobule through to the central vein. Note the presence of foreign-body giant cells in the parenchymal lesion and their absence in the periportal lesion. This type of lesion is very rare. × 50.

FIG. 6. A tuberculous lesion in a periportal space. Arrow points toward a bile duct, in the wall and lumen of which there are several leucocytes. × 100.

FIG. 7. Section of large bile duct showing normal mucosa on the right side and an erosion of the mucosa on the left, with extensive tuberculous inflammatory reaction involving this area. × 100.

FIG. 8. Section of the hepatic bile duct, showing a bile duct entering it. In this smaller bile duct there is a clump of leucocytes. × 100.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THE CALCIUM AND INORGANIC PHOSPHORUS CONTENT OF THE BLOOD SERUM IN TUBERCULOSIS

OBSERVATIONS ON PATIENTS UNDERGOING ALPINE LAMP TREATMENT[1]

MARION G. HOWE AND E. M. MEDLAR

Radiant energy has been claimed to be of great importance in maintaining a normal salt metabolism in the body, particularly of calcium and phosphorus. As is well known, a great deal of confirmatory work in this field has been done in connection with rickets, a disease characterized by a deficiency of ionic calcium, or ionic phosphorus, or both, in the blood.

Hess and Gutman (1) reported the first observations of chemical analyses of the blood of rachitic infants healed by sunlight. The arms and legs of the infants, sometimes the trunk, were exposed to direct sunlight from one-half hour to several hours daily during the summer months. The inorganic phosphorus of a series of bloods taken from these babies showed a gradual increase to normal as the rachitic signs diminished. The greatest increase of seven cases was 1.3 mgm. per 100 cc. over a period of 4 months, and the least was 0.5 mgm. There is some question whether their conclusions were wholly justified because it is not stated whether the patients were on an antirachitic diet or not.

Kramer, Casparis and Howland (2) observed an increase of inorganic phosphorus in the serum of five rachitic children, from as low as 2.5 and 3.2 to 6 mgm. per 100 cc. of blood after systematic exposure of from 4 to 8 weeks to the rays of the mercury-vapor-quartz lamp. In every instance there was healing of the rachitic process in the bones. The calcium increase was not as marked. At the same time the initial calcium was not as subnormal as the initial phosphorus. In one instance there was an increase from 8.5 to 10.3 mgm. per 100 cc. of blood. It is interesting to note that four of these children were colored and that

[1] From the John Rogers Hegeman Memorial Laboratory of the Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York.

the natural pigmentation of the skin did not prevent the effect of the rays.

Tisdall (3), reporting 6 cases of infantile rickets, showed in each instance an increase of both calcium and phosphorus after exposure to the mercury-vapor-quartz lamp. The distance between the lamp and the patient was 60 cm. and the length of time of a single exposure was usually 15 minutes. The shortest total length of time of exposure was $1\frac{1}{2}$ hours and the longest 7 hours. The greatest increase of calcium was 3 mgm. per 100 cc., the least 0.6 mgm., with an average of 1.4 mgm. The greatest increase for phosphorus was 3.9 mgm., the least 1.5 mgm., and the average 2.4 mgm. per 100 cc. of blood.

In addition to chemical investigations in connection with rickets and heliotherapy some work has been done relative to other pathological conditions. Casparis and Kramer (4) have treated 5 cases of active infantile tetany with radiations from the mercury-vapor-quartz lamp. The calcium of the serum was increased in every instance in from 3 to 7 days. The longest single exposure was 20 minutes. The inorganic phosphorus was raised to normal or above. Clinically, the tetanic symptoms disappeared and at the same time there was healing of the accompanying rachitic process.

Tisdall and Harris (5) have reported the inorganic phosphorus content of the serum of patients with bone tuberculosis after being exposed to the sun's rays all summer. The method of exposure is not stated. The radiograms showed deposition of new bone but the phosphate content was not elevated. The highest value for twelve cases was 3.9 mgm. per 100 cc. of blood. In two cases of soft-tissue tuberculosis the serum phosphorus was decreased about 1 mgm. per 100 cc. after exposure to 150 and 295 hours of sunlight. The series of a third case showed no marked change. Two cases of bone tuberculosis showed a decrease of 0.8 mgm. after 295 hours exposure to sunlight. A third remained the same.

Novak and Hollender (6) have studied the influence of ultraviolet irradiation on the calcium content of the blood serum in hay fever, hyperesthetic rhinitis and the asthmas. They have concluded that the ionic calcium of the blood serum is low in hyperesthetic rhinitis and certain cases of hay-fever and asthma; that "exposure to the mercury-vapor-quartz light, together with combined calcium-thyroid therapy, appears to fix permanently the ionic calcium content of the blood serum." Their

results are not reported in full. No figures are given to show that the radiations "fixed" the ionic calcium.

The metabolism of calcium in the tuberculous individual has always been of very great interest on account of the formation of calcified tubercles as a part of the healing process. Maver and Wells (7) found a marked tendency for accumulation of calcium in tuberculous tissues of guinea pigs when there was no calcification visible grossly or microscopically. Is the deposition of calcium a drain upon the supply, so that the concentration in the blood is kept at a low level, or is there a response to the need with an increased amount which may be stimulated by artificial means? One could hardly expect to find a marked variation from normal of the calcium concentration preparatory to or during the formation of these comparatively small calcified areas, when there is only a slight lowering or tendency to be low during the tremendous draft of pregnancy and lactation (8) (9). Halverson, Mohler and Bergeim (10) found that the values for serum calcium of tuberculous patients on a high milk diet were normal. The maximum variations were from 8.4 to 11.0 mgm. Sweany, Weathers and McCluskey (11) have reported findings which average somewhat higher, but they have considered them about normal. The concentration of calcium in the blood and also of phosphorus is remarkably constant (12) (13) (14) (15) (16) (17). Cats have been injected subcutaneously with nearly lethal doses of calcium chloride and a rise in the blood calcium thus produced. This reached its maximum in 30 to 90 minutes and fell again to normal within 5 or 6 hours (18). Such experimental overloading of the blood with calcium, followed by readjustment to normal, only emphasizes its constancy. In fact, it is just this limited range of values that makes any constant finding after a controlled therapy significant, a consideration of great importance in working with human subjects, many of whom are desperately ill.

The work here presented was undertaken to determine the effect of intensive quartz-lamp therapy upon the calcium and phosphorus content of tuberculous adults. Salvesen and Linder (19) believe, as a result of work done in connection with Bright's disease, that there are two calcium fractions in the blood, one diffusible and ionized, the other nondiffusible and probably bound to protein. In view of their observations the serum-protein has been determined in some cases at the beginning and end of treatment, to serve as a possible index to a disturbance in the equilibrium between these two calcium fractions.

The blood has been analyzed before and after treatment. In most instances examinations were made once or twice during the course.

Thirty-six of the patients were tuberculous. Five were being treated for skin affections and were nontuberculous. The serum from five normal individuals without light therapy was examined twice, separated in time by from 5 to 10 weeks.

TABLE 1

Normal controls

Ca and P, mgm. per 100 cc. serum

Protein, gm. per 100 cc. serum

CASE	DATE OF ANALYSIS	Ca	P	PROTEIN
	1924			
No. 1, F., age 34	Mar. 27	9.8	3.8	6.58
	May 29	10.9	4.1	6.73
No. 2, F., age 33	Mar. 18	9.8	4.0	7.07
	May 29	10.3		7.45
No. 3, F., age 31	Mar. 3	9.7 (average of 9.96, 9.57)	3.4	6.94
	Apr. 7	9.0	2.7	
No. 4, F., age 44	Mar. 3	10.3	3.1	
No. 5, M., age 38	Apr. 10	10.7 (average of 10.49, 11.03)	3.4	6.86
	May 19	10.3	3.4	7.41
No. 6, M., age 43	Apr. 10	10.1	4.5	7.13
	June 5	10.2	4.3	6.86

The source of the rays was the Alpine lamp which has a preponderance of the short ultraviolets shown by Hess and Weinstock (20) to be the effective zone. The current employed was 5 amperes. During entire courses subsequent to the first the intensifier was often used which increases the intensity of the rays about 20 per cent.

The routine for a course of 60 consecutive days was as follows:

DAYS	DISTANCE	MINUTES EXPOSURE, DORSAL AND VENTRAL (UNCOVERED)
1 through 12	30	3, increased by 3 every other day to 18
13–18	27	5, increased by 5 to 30
19–24	24	5–30
25–32	18	5–40
33–60	12	5–60 (last 17 days total of 2 hours each day)

TABLE 2

Nontuberculous group

Diseases of the skin

CASE	DIAGNOSIS	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
							days	*hours*	
		I							
No. 7, M., age 27	Mitral stenosis; eczema	Began Apr. 29	Apr. 29	11.0	3.4		0	0	Eczema improved
		Finished June 9	June 10	10.9	3.2		42	26.20	
		*June 9, 1:30–3 P.M.					42	26.20	
		I							
No. 8, M., age 36	Psoriasis	Began Mar. 31	Mar. 31	10.7	4.0	7.04	0	0	Psoriasis improved
		Finished June 2	May 2	11.3	2.9		28	12.00	
		*May 1, 11:35–12:05	(June 2						
		*June 1, 1–3	2 P.M.,	11.6	4.4			46.00	
			2:45 P.M.)	11.6	4.4		32	2.00	
							60	60.00	
		II							
No. 9, M., age 27	Psoriasis	With Intensifier	Jan. 21	10.7	3.5		0	0	Complete disappearance of lesions
		Began Jan. 1		(Average of					
		Finished Mar. 20		10.93					
		*Mar. 20, 1:15–3:15		10.55)					
			Feb. 21	10.6	4.7		31	15.86	
			Mar. 21	10.7	3.7		29	46.32	
							60	62.18	

		I							
No. 10, M., age 48	Muscular rheumatism; acne vulgaris	Began Nov. 3	Nov. 2	9.4			0	0	
		Finished Jan. 1	Nov. 23	9.6 (Average of 9.94 9.36)	3.6		20	9.40	Improved
			Dec. 14	10.6			21	16.50	
			Jan. 3	9.9	3.4		19	37.50	
							60	63.40	
		I							
No. 11, M., age 47	Psoriasis	Began Dec. 14	Dec. 14	10.6	4.8		0	0	Definitely improved
		Finished Mar. 12	Jan. 11	10.0	4.1		28	12.80	
		*Mar. 12, 9:20–11:20	Feb. 11	9.8	4.1		30	26.50	
			Mar. 13	10.3	3.4	6.06	31	59.50	
							89	98.80	
		II							
		With Intensifier	Apr. 17	9.9		5.57	0	0	Skin lesions and general condition somewhat improved
		Began Apr. 18	(June 10						
		Finished June 10	7:45 A.M.	10.0	3.5		53	48.20	
			11 A.M.)	10.1	3.5	6.74	1	2.00	
							54	50.20	

* Time of last treatment preceding blood analysis.

TABLE 3

Tuberculous group

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
				Suspected					
							days	*hours*	
		II							
No. 12, F., age 24	Hysteria	Began Oct. 31	Oct. 30	10.3			0	0	
		III							
		Began Feb. 11	Feb. 11	10.0	3.6		0	0	General condition definitely improved
		*Finished Apr. 10	Apr. 11	10.3	3.4		60	62.62	
		*Apr. 10, 1:50–2:50					60	62.62	
				Incipient					
		I							
No. 13, F., age 35	Chronic appendicitis	Began Dec. 20	Dec. 18	10.8	4.4		0	0	None
		Finished Jan. 14	Jan. 15	10.3	3.8		26	11.66	
							26	11.66	
		I							
No. 14, F.		Began Dec. 11	Dec. 10	9.7	4.1		0	0	None
		Finished Jan. 23	Jan. 15	10.4	4.3		31	15.86	
							31	15.86	
		I							
No. 15, F., age 21	Tuberculosis of cervical lymph node	Began Oct. 11	Oct. 16	9.8			5	0.90	Enlarged cervical gland very much improved
		Finished Dec. 9	Nov. 6	9.4			21	10.80	
			Dec. 10	9.9	3.8		34	50.51	
							60	62.20	

		II							
		With Intensifier	Mar. 18	10.5	4.0		0	0	General condition markedly improved; adenitis practically gone
		Began Mar. 18	May 19	10.9	3.5		59	54.70	
		Finished May 17		(Average of 11.13 10.74)			59	54.70	
				Moderately advanced					
		I							
No. 16, F., age 33	Healed miliary tuberculosis of the lungs	Began Oct. 11	Oct. 16	9.9			5	0.90	General condition improved
		Finished Dec. 10	Nov. 6	9.8			21	10.80	
				(Average of 10.14, 9.46)					
			Dec. 10	10.3	3.6		31	37.82	
							57	49.52	
		II							
		With Intensifier							
		Began Jan. 25	Jan. 25	10.2	3.3		0	0	General condition improved
		*Mar. 25, 3:25–5:25		(Average of 10.06, 10.44)					
			Mar. 27	10.6	3.6	7.24	60	61.36	
							60	61.36	
		I							
No. 17, F., age 18		Began Mar. 9	Mar. 6	10.1	4.1		0	0	General condition slightly improved
		Finished June 8	Apr. 7	10.5	4.7		29	13.70	
			June 9	10.7	4.6		43	38.16	
							72	51.86	

TABLE 3—*Continued*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
				Moderately advanced—Continued					
							days	*hours*	
		I							
No. 18, F., age 25		Began Feb. 11	Feb. 11	9.7	3.8		0	0	General condition slightly, but definitely improved
		Finished Apr. 10	Apr. 11	10.3	3.7		58	55.70	
		*Apr. 10, 1:45–3:45					58	55.70	
		I							
No. 19, M., age 26		Began Dec. 1	Nov. 30	10.7	3.04		0	0	Definitely improved
		Finished Jan. 29	Dec. 31	9.9			30	14.04	
			Feb. 1	10.1	3.09		30	45.32	
				(Average of 10.35, 9.96)			60	59.36	
		II							
No. 20, F., age 31		With Intensifier Began Dec. 1	Nov. 30	10.1	3.8		0	0	General condition improved
		Finished Jan. 29		(Average of 10.33, 9.94)					
			Dec. 31	10.2			30	13.86	
				(Average of 10.45, 10.07)					
			Feb. 1	10.1	3.2		30	46.50	
							60	60.36	

		III							
		With Intensifier	Mar. 25	10.3	3.5	6.67	0	0	General condition slightly
		Began Mar. 25	May 26	10.4	3.9	7.61	60	62.20	improved
		Finished May 24					60	62.20	
		*May 24, 3:05–5:05							
		II							
No. 21, F., age 20	Tuberculosis of larynx	With Intensifier	Mar. 6	10.1	4.1		0	0	General condition somewhat
		Began Mar. 9	Apr. 7	10.6	3.8		29	13.70	improved; larynx probably
		Finished May 7	May 8	10.8	4.0		31	48.50	improved
		*Apr. 6, 6:30–7:20 A.M					60	62.20	
		*May 7, 8–9 A.M.							
		I							
No. 22, F., age 22		Began Dec. 27	Dec. 28	9.7	3.3		1	0.10	General condition markedly
		Finished Feb. 25	Jan. 29	10.3	4.2		31	17.10	improved
			Feb. 26	10.3	3.6		28	45.00	
							60	62.20	
		III							
No. 23, F., age 44	Tuberculosis of ilium	Began Dec. 27	Dec. 28	9.7	3.3		1	0.10	General condition improved;
	Tuberculosis of femur	Finished Feb. 24	Jan. 29	9.8 (Average of 9.57, 10.06)	3.5		32	17.36	abscess not discharging as much as formerly
			Feb. 26		3.7		27	44.82	
							60	62.28	

TABLE 3—*Continued*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
				Moderately advanced—Continued					
							days	*hours*	
		IV							
		Began Apr. 3	Apr. 3	11.3		7.96	0	0	Improved
		Finished June 3		(Average of					
		*May 9, 1–1:50		11.52,					
		*June 3, 3:05–5:05		11.18)					
			May 10	10.3	4.5	7.75	37	19.70	
			June 5	10.0	4.0		22	36.00	
							59	55.70	
		I							
No. 24, M., age 25	Tuberculosis of intestine	Began Nov. 16	Nov. 16	9.9	3.3		0	0	Marked general improvement, with disappearance of intestinal symptoms
		Finished Jan. 14	Dec. 7	9.7			21	9.90	
			Jan. 15	10.1	4.0		39	52.82	
							60	62.72	
		V							
No. 25, F., age 26		With Intensifier	Mar. 6	10.3	3.9	7.78	0	0	General condition slightly improved
		Began Mar. 9	Apr. 7		4.0		30	13.70	
		Finished June 8	Jan. 9	11.7	3.7		58	97.32	
		*Apr. 6, 12:45–1:35		(Average of			88	111.02	
		*June 8, 3:05–5:05		11.91,					
				11.52)					
		II							
No. 26, F., age 24		With Intensifier	Nov. 30	10.4	3.3		0	0	
		Began Dec. 1		(Average of					
		Discontinued		10.14,					
				10.73)					

		III							
		With Intensifier	Feb. 21	9.9	4.2		0	0	General condition improved
		Began Feb. 22	Mar. 21	10.4	4.5		28	12.86	
		Finished May 31	June 2	10.4	4.0		72	129.32	
							100	142.18	
		II							
No. 27, F., age 27		With Intensifier	Feb. 21	10.4	3.8		0	0	Improved
		Began Feb. 22	Mar. 21	10.6	3.8	7.50	28	12.86	
		Finished May 31	June 2	10.8	3.6	7.55	72	129.32	
							100	142.18	
				Far advanced					
		III							
No. 28, M., age 25	Tuberculosis of larynx	Began Dec. 25	Dec. 28	9.6	3.5		1	0.10	None
		Finished Jan. 15	Jan. 17	10.0	3.1		19	8.10	
							20	8.20	
		IV							
		Began Mar. 13	Mar. 13	10.3	3.3		0	0	Unimproved
		Finished Apr. 22	Apr. 22	10.7	4.0		40	23.20	
		*Apr. 21, 9:05–10:25					40	23.20	
		II							
No. 29, F., age 34		Began Oct. 2	Oct. 18	9.6 (Average of 9.36, 9.86)			16	5.08	
		Finished Dec. 18	Nov. 9	8.4 (Average of 8.27, 8.67)			18	13.10	
							34	18.18	

TABLE 3—*Continued*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
							days	*hours*	
Far advanced—Continued									
		III							
No. 30, F., age 19		With Intensifier	Jan. 3	10.2			0	0	
		Began Jan. 3	Feb. 7	10.5	3.3		35	18.20	
		Finished Mar. 2					35	18.20	
		IV							
		Began Apr. 3	Apr. 3	10.1	6.5	7.46	0	0	General condition slightly improved
		Finished June 1	June 2	10.5	4.0	7.62	60	62.20	
		*June 1, 3–5					60	62.20	
		I							
No. 31, F., age 19		Began Nov. 3	Nov. 2	9.9			0	0	
		Finished Dec. 27	Nov. 23	10.1	3.6		20	9.40	
			Dec. 14		4.5		21	16.50	
							41	25.90	
		II							
		With Intensifier	Mar. 18	10.9	4.2		0	0	General condition slightly improved
		Began Mar. 18	Apr. 17	10.7	4.6		30	14.70	
		Finished May 18	May 19	11.6	4.0		28	34.50	
		*Apr. 16, 1:50–2:50		(Average of			58	49.20	
		*May 18, 2:35–4:35		11.91, 11.36)					

		II							
No. 32, F., age 30	Tuberculosis of larynx? Tuberculosis of intestine?	Began Feb. 1	Feb. 1	9.5	4.3		0	0	General condition improved
		Finished Mar. 26	Mar. 3	9.7	4.4	6.66	28	12.86	
		*Mar. 2, 8:15–9:15 A.M.	Mar. 31	10.4 (Average of 10.74, 10.25)	4.5	7.48	24	27.00	
							52	39.86	
		III							
		Began Apr. 22	Apr. 22	10.5	4.6	7.36	0	0	General condition and intestinal complication improved
		Finished June 9	June 10	10.0	3.7	8.20	49	36.20	
							49	36.20	
		V							
No. 33, F., age 34	Tuberculosis of larynx; tuberculosis of intestine	Began Sept. 11	Oct. 18	10.6			37	40.70	
							37	40.70	
		VI							
		With Intensifier	Jan. 25	10.4	3.3		0	0	Somewhat improved
		Began Jan. 25	Mar. 25	11.0	3.9	7.98	60	62.20	
		Finished Mar. 24							
		*Mar. 24, 3:10–5:10					60	62.20	
		VII							
		With Intensifier	Apr. 17	9.8 (Average of 9.67, 10.09)	3.3		0	0	
		Began Apr. 17							

TABLE 3—*Continued*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
				Far advanced—Continued					
							days	*hours*	
		I							
No. 34, M., age 37	Tuberculosis of larynx; tuberculous fistula in ano	Began Oct. 17 Finished Dec. 15	Oct. 18 Nov. 6	10.5 9.1 (Average of 9.36, 8.96)			1 19	0.10 8.10	Larynx and general condition improved
			Nov. 28	9.7	3.2		22	17.50	
			Dec. 10	10.4 (Average of 10.76, 10.05)	2.9		12 54	23.00 48.70	
		II							
No. 35, M., age 31	Tuberculosis of peritoneum	Began Nov. 29 Finished Feb. 9	Nov. 30 Dec. 28	9.8 10.0	3.2		1 20	0.10 8.30	Slightly improved
			Feb. 11	10.4	3.8		38 59	43.32 51.72	
		III							
		Began Mar. 25 Discontinued	Mar. 24	10.3	4.1		0	0	
		I							
No. 36, M., age 32	Tuberculosis of larynx; tuberculosis of intestine	Began Oct. 23 Finished Dec. 21	Oct. 26 Nov. 16	11.0 9.9 (Average of 10.33, 9.56)	3.9		3 21	0.40 11.20	General condition and complications improved

			Dec. 7	9.9 (Average of 10.65, 9.17)	3.9	21	20.32	
			Dec. 18		3.6	11	21.32	
						56	53.24	
		II						
		With Intensifier						
		Began Feb. 1	Feb. 1	10.7	4.0	0	0	Slightly improved
		Finished Mar. 31	Apr. 3	11.6	4.4	59	62.00	
		*Mar. 31, 8–10 A.M.				59	62.00	
		II						
No. 37, M., age 28	Tuberculosis of intestine	Began Feb. 11	Feb. 11	10.0	3.4	0	0	General condition definitely improved; disappearence of intestinal trouble
		Finished Apr. 11	Apr. 11	10.4	3.3	59	56.70	
		*Apr. 10, 2:55–4:55				59	56.70	
		I						
No. 38, M., age 29	Tuberculosis of intestine	Began Dec. 1	Nov. 30	9.9	3.0	0	0	General condition improved
		Finished Feb. 4	Dec. 28	9.8	3.5	24	11.20	
			Feb. 7	10.8	3.9	35	45.50	
						59	56.70	
		II						
		With Intensifier	Feb. 14	10.2	3.6	0	0	Condition apparently improved
		Began Feb. 20	Apr. 22	10.3	3.9	60	62.20	
		Finished Apr. 19				60	62.20	

TABLE 3—*Continued*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
			Far advanced—Continued						
							days	*hours*	
		I							
No. 39, M., age 25	Tuberculosis of larynx; tuberculosis of intestine	Began Nov. 30	Nov. 30	9.4	3.9		0	0	General condition markedly improved
		Finished Jan. 28	Dec. 31	9.7			31	15.02	
			Jan. 29	9.7			29	43.00	
							60	58.02	
		II							
		With Intensifier	Mar. 6	9.5	4.2		0	0	Intestinal involvement slightly improved
		Began Mar. 9	May 8	10.1	4.3		60	58.66	
		Finished May 7					60	58.66	
		I							
No. 40, F., age 19		Began Apr. 10	Apr. 10	10.1	5.1	6.86	0	0	General condition slightly improved
		Finished June 6	June 6						
		*June 5, 8–10 A.M.	(9 A.M.	10.4	5.2		57	56.20	
			11 A.M.)	10.5	4.8		1	2.00	
							58	58.20	
		I							
No. 41, M., age 33	Tuberculosis of larynx; tuberculosis of intestine	Began Oct. 2	Oct. 16	10.4 (Average of 10.75, 10.14)			14	4.70	General condition and complications improved
		Finished Nov. 30	Nov. 6	10.0			21	15.16	
			Nov. 30	11.3		2.4	24	39.16	
							59	59.02	

		II							
		With Intensifier	Jan. 11	9.7	2.7		0	0	General condition and complications improved
		Began Jan. 11	Feb. 14	10.2	2.9		34	18.20	
		Finished Mar. 11	Mar. 13	9.9	2.5		26	42.82	
		*Mar. 11, 6:30–8:30 P.M.					60	61.02	
		V							
No. 42, M., age 30	Tuberculosis of intestine; eczema	Began Oct. 20	Oct. 18	10.6			0	0	General condition very much improved; eczema cured
		Finished Dec. 18	Nov. 9	8.1			20	8.20	
			Nov. 28	8.5	4.3		19	14.00	
			Dec. 18	10.2	3.9		20	38.50	
							59	60.70	
		VI							
		With Intensifier	Jan. 11	9.7	3.8		2	0.20	None
		Began Jan. 9	Mar. 6	9.8	4.2	6.11	53	37.82	
		Finished Mar. 8					55	38.02	
		*Mar. 5, 12:45–1:25							
		*Apr. 16, 11:10–11:46							
		VII							
		Began Apr. 5	Apr. 17	10.0	4.5		12	4.20	None
		Discontinued					12	4.20	
		I							
No. 43, M., age 26	Tuberculous fistula in ano	Began Jan. 17	Jan. 17	10.6	3.3		0	0	General condition markedly improved; complication slightly improved
		Finished Mar. 17	Feb. 14	10.5	2.8		27	12.20	
		*Mar. 17, 1–3	Mar. 18	11.1	3.3	7.75	33	50.00	
							60	62.20	

TABLE 3—*Concluded*

CASE	COMPLICATION	COURSE	DATE OF ANALYSIS	Ca	P	PROTEIN	TREATMENT		CLINICAL RESULT OF TREATMENT
				Far advanced—Continued					
							days	*hours*	
		II							
No. 44, F., age 23		Began Nov. 3	Nov. 2	9.3			0	0	Condition very much improved
		With Intensifier	Nov. 23	9.9	3.7		20	7.60	
		Beginning Jan. 2		(Average of					
		Finished Jan. 31		9.76,					
				10.14)					
			Feb. 1	10.5	5.7		70	65.66	
							90	73.26	
		III							
		With Intensifier	Mar. 18	9.7	4.4		0	0	General condition slightly improved
		Began Mar. 18	May 19	10.4	3.7		60	62.20	
		Finished May 16					60	62.20	
		*May 16, 8:05–10:05							
		I							
No. 45, F., age 35	Tuberculosis of intestine	Began Mar. 13	Mar. 13	9.7	3.9	7.76	0	0	General and intestinal condition improved
		Finished May 26		(Average of					
				9.57,					
				9.96)					
			Apr. 17	9.9		6.84	35	18.20	
			May 26	11.2	3.9	7.08	35	56.50	
							70	74.70	

		VII							
No. 46, F., age 21	Tuberculosis of intestine; tuberculosis of larynx	Began Sept. 11 Finished Nov. 9	Oct. 18 Nov. 9	10.2 8.3 (Average of 8.67, 8.07)			37 22 59	42.06 44.00 86.06	Apparently arrested
		VIII							
		With Intensifier Began Feb. 27 Finished May 24 *May 24, 1–3	Jan. 25	10.0 (Average of 9.76, 10.24)		3.4	0	0	Improved
			May 26	10.6	3.5		88 88	118.20 118.20	
		II							
No. 47, F., age 20	Tuberculosis of intestine?	With Intensifier Began Jan. 3 Finished Apr. 1 *Apr. 1, 12:45–2:45	Jan. 3 Feb. 7 Apr. 3	9.4 9.6 10.1	3.3 4.0 3.8		0 35 55 90	0 9.10 104.00 113.10	Slightly improved

* Time of last treatment preceding blood analysis.

If the patient was burned or his temperature elevated, treatment was discontinued. When resumed the schedule was of necessity modified so that the increase of time was always gradual.

Ten to 15 cc. of blood was drawn by syringe in the morning before breakfast and transferred to a 15 cc. graduated centrifuge tube. After standing for about one-half hour, the blood was centrifugated. As much clear serum was decanted as possible. Then the remaining serum with cells was poured into a second clean, dry tube and the contents centrifugated until the serum could be decanted or drawn off with a pipette. The calcium was determined by the direct precipitation method of Kramer and Tisdall (21) (22). If two determinations on the same serum did not check within 0.3 mgm., the results of both determinations are given in the table. The inorganic phosphorus was determined by Briggs's first modification (23) of the Bell-Doisy method. Duplicates, which were always satisfactory, were performed whenever possible. The method is such that familiarity with it obviates the necessity for duplicates in every case. The total protein nitrogen of the serum was estimated after determining the total nitrogen and the nonprotein nitrogen. One cubic centimetre of serum was diluted with 0.8 per cent sodium chloride by 30 to 75 times its volume and a micro-Kjeldahl performed on 1 cc. of the diluted serum. A few drops of hydrogen peroxide were used to facilitate the final oxidation. The total nitrogen was done in duplicate or triplicate. The nonprotein nitrogen was determined on the tungstic acid filtrate of Folin and Wu (24). In both the total nitrogen and the nonprotein nitrogen the ammonia was aerated and the contents of the receiving tube nesslerized.

The foregoing tables 1 to 3 give the results of the chemical determinations together with data of value from the clinical side.

DISCUSSION

The most striking feature of these data is the similarity of any one series to any other series irrespective of length of time of exposure to the rays or condition of subject.

In order to ascertain whether the rays brought about a temporary increase, which adjusted itself to normal before the following morning, when the blood was always taken, examinations were made in three cases before and after treatment. The second blood of case 8 was analyzed 20 minutes after a 2-hour treatment. The first blood was taken

1½ hours after the noon meal. The second blood of cases 11 and 40 was examined 1 hour after a 2-hour treatment. No food had been taken since the preceding evening meal. The values were constant.

The figures for serum-protein do not reveal any evidence of disturbed balance between the diffusible calcium and the protein-bound calcium.

The *modus operandi* of the ultraviolet rays is not known. Hess (25) had made the statement that a "chemical change, which may be significant, takes place in the blood in the course of heliotherapy." Park (26), in his excellent review of the rickets problem, wrote that the sun's rays or their equivalent exert "a stimulatory or a regulatory influence on the metabolism of the body, in particular of the calcium and phosphorus." Orr, Holt, Wilkins and Boone (27) have advanced the very interesting theory that the ultraviolet rays are effective because they increase the absorption of calcium and phosphorus from the intestine. They have shown that the retention of calcium and phosphorus in rachitic cases in which the diet was adequate has been greatly improved after exposure to ultraviolet rays without changing the diet. Since the rays cannot penetrate to the absorptive membrane of the intestine they must initiate a change, or perhaps a series of changes, through their action on the skin or the blood near the surface.

The fact that the rays do ensure a better retention of calcium in cases of rickets, in which the concentration is subnormal, but apparently do not increase the absorption if the concentration is normal (note particularly cases 11, 26 and 47), would seem to show that the increase of calcium and phosphorus is but one manifestation of their beneficial effect. Many of the patients who were under observation, whether tuberculous or nontuberculous, were greatly benefited by the therapy, but neither the need for such treatment nor the explanation of the gratifying clinical results can be found in an altered metabolism of calcium or phosphorus.

CONCLUSIONS

1. There is no evidence of an abnormal metabolism of calcium or phosphorus in the tuberculous patient.

2. There is no evidence of ultraviolet rays having any effect upon the calcium or phosphorus content of the blood, granted their concentration is within normal limits before treatment.

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THE VALUE OF ERYTHROCYTE SEDIMENTATION DETERMINATIONS IN PULMONARY TUBERCULOSIS[1]

W. H. MORRISS

In the treatment of patients with pulmonary tuberculosis, it is extremely important that the clinician should be able to estimate activity, for largely on this estimation will depend the prescription of rest and exercise. The observation of temperature and pulse is undoubtedly of the greatest importance in this respect; but to make temperature and pulse the sole guides will certainly lead to many mistakes. Gain of weight and strength, and the disappearance of symptoms, such as cough, expectoration and undue fatigue, are encouraging developments, but none of them offers definite objective evidence of inactivity. Unfortunately, no reliable test for activity is at hand and judgment must be attained by careful observation of each case, and finally by the experimental method of testing the patient's reaction to small allotments of exercise.

Several workers in tuberculosis on the continent have employed, in the study of their patients, the Fahraeus erythrocyte sedimentation test with interesting results, and report that it offers a valuable help in the estimation of activity. It was with this point in mind that we have used the test for the last few months at the Gaylord Farm Sanatorium on all our patients, and our results have proved of sufficient interest to justify a preliminary report, though the work has not been carried on long enough to form an exact estimate of its value.

When citrated blood is allowed to stand the erythrocytes settle down, leaving clear plasma above. Fahraeus (1) noted first that the velocity of this sedimentation varies under certain physiological conditions. It is somewhat greater in women than in men. It is increased with menstruation and in the later half of pregnancy. Other authors have studied the reaction from different points of view, with the result that the velocity is found to be accelerated under a variety of pathological conditions;

[1] From the Gaylord Farm Sanatorium, Wallingford, Connecticut.

thus, it is increased in acute infections, especially when the temperature is high; also in most chronic infections and in cases of malignant tumor. Syphilis, arteriosclerosis, chronic arthritis, tabes and many psychoses cause a definite increase in the velocity of sedimentation. Westergren (2), Müller (3), Ritter (4), Katz (5), and Dreyfus and Hecht (6) in Germany, Delhaye (7) in France, and Levinson (8) in Chicago, have studied the reaction in tuberculosis. In the article of the latter author an excellent résumé of the rather extensive literature on the subject is to be found. In general, most of the authors agree that the velocity of sedimentation is definitely increased in active pulmonary tuberculosis, that the increase seems to run parallel with the amount of pathological change which has taken place in the lungs, that it is highest in the acutely progressive stages, and that a determination of the velocity is of some value in prognosis.

TECHNIQUE OF TEST

Several different methods of performing the test have been described. Thus, Fahraeus collects citrated blood in test tubes, 17 cm. in length and 9 mm. internal diameter, measuring the height of the column of clear plasma above the erythrocytes at one, two and twenty-four hours; Linzenmeier (9) employs short tubes, 6.5 cm. long and of 5 mm. internal diameter, and with a mark to indicate 1 cc. of blood and a second mark 18 mm. below the first. The reading is made by noting the time at which the level of the erythrocytes reached the second mark. Westergren collects the blood in small record syringes, diluting four parts of blood with one part of 3.8 per cent sodium citrate. The blood is then drawn up into pipettes of about 300 mm. height and 2.5 mm. internal diameter and readings made in mm. of the degree of fall of the erythrocytes at one, two and twenty-four hours.

Several other methods are described which employ slight modifications of the methods already mentioned. The method of Westergren, as it gives a high column and employs a small amount of blood, seemed preferable. In our work the blood was collected from an arm vein in a record syringe containing enough 3.8 per cent sodium-citrate solution to give a one to four dilution, carried from the ward to the laboratory in small Wassermann test-tubes and drawn up into 1 cc. pipettes. It was found difficult to obtain tubes of a uniform internal diameter of 2.5 mm.; therefore calibrated 1 cc. pipettes were used, the readings being made on the pipette scale after filling the pipette exactly to the 1 cc.

mark, stoppering it with a bored-out rubber cork and placing it on a rack. In this way readings made at one, two and twenty-four hours represented definite percentages of the total volumes of blood, and simplified considerably a comparison of values.

On a series of 100 cases, readings were made every fifteen minutes for several hours and the results charted in graphs. It was seen that the most significant part of the curve occurred within two hours and that the reading made at two hours offered the best single comparison, though the entire curve was probably of some importance. It was found that tubes of even smaller diameter could be employed with practically identical results. In 50 cases, 0.1 and 0.2 cc. pipettes were so used, and the readings found to agree very closely with those made in the 1 cc. pipettes. As it is at times difficult to obtain blood from the arm vein and as venupuncture is never a procedure enjoyed by the patient, it was hoped that a technique could be devised employing so little blood that it could be obtained from the finger, as in making a blood count. This is being tried out in a series of cases and seems to work fairly satisfactorily, provided the blood is allowed to flow without any pressure on the surrounding tissues.

In this study 150 patients have been tested, including 12 far advanced, 88 moderately advanced, 20 minimal, and 10 patients in which a diagnosis of no clinical tuberculosis was made.

The variety of methods employed by the various authors makes it difficult to compare the readings and therefore necessary to determine for each method its own normal standards.

NORMAL STANDARDS

The blood of 21 normal men and women was examined to determine a normal standard, and the results are shown in table 1.

Normal two-hour readings in the male are found to lie between the values of 1 and 5 per cent, and in the female between 5 and 10 per cent.

INFLUENCE OF THE EXTENT OF LUNG INJURY

The series has been grouped according to the classification of the National Tuberculosis Association into minimal, moderately advanced, and far advanced.

TABLE 1

Normal values for men and women

SERIAL NUMBER	1 HOUR	2 HOURS	24 HOURS	REMARKS
Men				
16	0.5	1	17.5	No clinical tuberculosis; diagnostic case
99	1.25	4.5	33	Hospital orderly
120	1.5	3.5	23.5	Hospital mechanic
132	1.5	3.5	22	Hospital orderly
79	0.3	1.5	16	Normal male
126	2.5	7	27	No clinical tuberculosis
127	1	2.5	27.5	No clinical tuberculosis
138	3	7.5	36.5	Hospital orderly
131	3	7.5	28	No clinical tuberculosis
78	0.5	1.25	19	No pulmonary tuberculosis
151	2.25	6.5	34.5	Normal male
Women				
104	2.5	6.5	37.5	No clinical tuberculosis
12	3.0	8	41	Nurse
35	2	6	25	No clinical tuberculosis
113	2.25	6.5	35.25	Nurse
124	2	5.75	36.5	Nurse
142	2.5	6.5	39.5	Nurse
146	1.75	4.75	35	Hospital maid
149	3	8.5	39	Office work
115	2.25	6	20	Healed cervical adenitis
148	4.5	11.5	47	Secretary

TABLE 2

National Tuberculosis Association classification

		NUMBER OF CASES	READING 0–10	READING 10–20	READING 20–30	READING 30–	PERCENTAGE ABOVE 20
Minimal	Male	8	7	0	1	0	12.5
	Female	12	5	2	3	2	41.6
Moderately advanced	Male	50	20	12	8	10	36
	Female	38	4	9	10	15	65.7
Far advanced	Male	11	1	3	2	5	63.6
	Female	1	0	0	0	1	100
No clinical tuberculosis	Male	7	5	1	0	1	14.3
	Female	3	2	1	0	0	0

Table 2 shows the number of cases of each group in column three and in the following columns the number of cases that fell within certain two-hour reading limits.

While the values tend to be slightly higher where several lobes are affected, several of our patients with very extensive pulmonary lesions gave readings within normal limits, and there are so many exceptions to this rule that no estimate of the extent of the lesion can be formed by a determination of the sedimentation velocity.

TABLE 3

Febrile cases

SERIAL NUMBER	TEMPERATURE RANGE	PULSE RANGE	1 HOUR	2 HOURS	24 HOURS	REMARKS
1	99–101	86–110	30	51	63.5	Very active
4	99–100	96–108	16	31	58	Bed
5	98–99.8	92–100	20	31	55.5	Bed
6	99–102	108–120	36	47	64	Very active
7	99–99.6	84–100	46	59	64.5	Bed
9	98–99.5	100–110	19	47	55	Bed
10	99–99.6	110–120	43	60	65	Active; progressive
13	97–99.6	100–110	16	32	52.5	Bed
14	98–98.8	110–124	32	50	60	Small hemoptyses
25	98–99.8	104–120	49	60	65	Progressive
26	98–99.6	104–120	22.5	41	61	Bed
29	98–99.4	112–120	29	49	62	Bed
34	99–102	110–130	45	61	70	Complication pyelitis
36	98–99.4	108–116	33	48	62	Bed
38	99–100.4	96–110	8	21	72	Progressive
67	98–100.2	96–120	26	43	59	Bed
80	98–99.8	96–100	21	44	61	Bed
92	101–104	94–110	38	52	63	Pneumonia
129	98–99.6	90–110	19	34	55	Bed
136	98–99.8	90–116	38	55	64	Up 2 meals

SEDIMENTATION VELOCITY AS AN EVIDENCE OF CLINICAL ACTIVITY

While it is realized that there is no perfectly definite criterion by which patients may be grouped as active or inactive a rough separation of these two groups can be made and our patients have been so grouped according to whether the following indicating sign was present or absent: (1) elevation of temperature and pulse, (2) positive sputa, (3) loss of weight, (4) presence of râles, and (5) reaction to exercise.

As shown in table 3 all of the 20 patients with definite elevation of temperature and pulse gave a distinctly high reading, 19 of them being

over 30 per cent. Without exception, all of the very high readings occurred in this group. Elevation of temperature and pulse is probably always associated with a markedly increased velocity of sedimentation.

In table 4 are grouped the patients whose sputum contained tubercle bacilli, those whose sputum was negative at the time but had previously been positive and those whose sputum was persistently negative or who did not expectorate.

TABLE 4

Positive and negative sputa

	NUMBER	0–10	10–20	20–30	30–	PERCENTAGE ABOVE 20
Sputum positive	52	7	11	11	23	65.3
Negative; previously positive	29	13	11	3	2	17.2
Negative; no expectoration	35	18	5	7	5	34.3

TABLE 5

Loss of weight

	NUMBER	0–10	10–20	20–30	30–	PERCENTAGE ABOVE 20
Losing weight and below standard	11	1	1	3	6	81.8
Stationary; below standard	16	1	3	4	8	75

TABLE 6

Absence of râles

	NUMBER	0–10	10–20	20–30	30–	PERCENTAGE ABOVE 20
No râles	20	17	1	2	0	10

While there are numerous exceptions to the rule, as might have been expected, the higher readings are found to occur in the group with positive sputa and the percentage of normal or low readings is much larger in the group with negative sputa.

Table 5 shows the group of patients exhibiting an unsatisfactory weight chart. All of the patients who are losing weight have given readings of high value, while those whose weight is stationary at a point below normal also show a definitely high group of determinations.

Table 6 comprises 20 patients without râles on physical examination. There is here a marked grouping in the low levels; only 10 per cent have given readings above 20 per cent.

Table 7 offers a contrast between a group of patients apparently quiescent, who are taking at least two hours exercise a day, and a group of patients afebrile, but still considered active and not yet started on exercise. Of the active patients, 63.3 per cent show readings above 20 per cent, while in the other group only 10.8 per cent are above 20 per cent.

It is apparent that those patients who exhibit definite evidence of clinical activity show, almost without exception, high values for sedimentation velocity, while with a few exceptions those patients considered practically quiescent give low values. As an indication of clinical activity the test seems of considerable value.

TABLE 7

Contrast on basis of exercise

	NUMBER	0–10	10–20	20–30	30–	PERCENTAGE ABOVE 20
Patients without exercise	30	5	6	11	8	63.3
Patients with over 2 hours exercise	37	24	9	3	1	10.8

TABLE 8

Cavities and artificial pneumothorax

	NUMBER	0–10	10–20	20–30	30–	PERCENTAGE ABOVE 20
Cavities	11	1	2	3	5	72.7
Pneumothorax	9	3	3	1	2	33.3

Patients under treatment by artificial pneumothorax were examined and the results charted in table 8. No conclusion can be drawn from this small series, though it may well be that the test may prove of value in estimating the success of this treatment.

The small number of patients who exhibited definite X-ray and physical-examination evidence of cavitation were grouped with the result shown also in table 8. While it is stated by several authors that patients with cavities always give a high reading this is seen not to be the result in some of our cases.

VALUE OF THE TEST IN PROGNOSIS AND DIAGNOSIS

It is claimed by some authors (Delhaye, Dreyfus and Hecht) that the test has great value in estimating prognosis. Thus Delhaye states that a very high reading is always of grave significance; for while it may

decrease under treatment it always rises again, and the outcome is invariably fatal. On the other hand, Müller states that he has found the test valueless as regards prognosis. To determine this point a much longer experience with the test is necessary and no conclusion can be drawn at present from our brief series.

One case, however, was interesting in this regard. At the time the test was made the patient was afebrile, and apparently doing well; she was taking fifteen minutes' exercise twice a day, gaining slightly in weight, and showed marked amelioration of the cough and expectoration with which she entered. Her test, however, showed a two-hour reading of 32 per cent. About two weeks later she had a severe relapse, with high fever, pleurisy and marked increase in both cough and expectoration. Her second test made during the height of the attack showed the high level of 52 per cent at the second hour. In all fairness it must be stated, however, that several other women patients who apparently were improving showed equally high determinations and so far have failed to relapse.

We have not as yet had the opportunity to repeat many of the tests on the same individual, and therefore cannot corroborate Delhaye's statement that the sedimentation value in acutely active cases that are improving falls much later than temperature and pulse. One patient, who made marked improvement after exhibiting very acute symptoms, showed a fall from 51 to 32 per cent in the two-hour reading, and a second gave the same reading of 41 per cent after two and a half months of bed treatment, during which time she had made some clinical improvement but still had slight elevation of temperature and pulse.

As regards diagnosis, little has been claimed for the test. It is nonspecific and is influenced by a large variety of pathological conditions. It is perhaps fair to state that an entirely normal reading makes a definite active pulmonary tuberculosis extremely unlikely. An abnormally high reading in a suspected case, provided that the obvious misleading factors, such as pregnancy, syphilis, and chronic infection, can be ruled out, makes the diagnosis of tuberculosis likely, but by no means certain. Ritter considers that the test may be employed safely as a criterion by which to judge the necessity of treatment.

DISCUSSION

Numerous explanations of the varying rate of sedimentation of erythrocytes have been advanced by different investigators, and as mentioned above, an excellent résumé of this literature is to be found in Levinson's paper.

In general, three elements which influence the phenomenon are to be considered.

(*1*) *The composition of the plasma:* Westergren has shown that sedimentation of erythrocytes is very rapid in a solution containing relatively large amounts of fibrinogen, slower in globulin, and much slower in albumin or normal saline. Levinson (8) found a definite increase in plasma fibrinogen in active pulmonary tuberculosis, and this has been found also true in pregnancy. Several other authors have done work which seems to indicate that the content of fibrinogen in the plasma is a most important factor. The presence of antibodies in the plasma has also been suggested as a factor of importance (Leendertz (10)).

(*2*) *The volume, physical and chemical composition of the erythrocytes* may also influence the rate of sedimentation. Marloff (11) has shown that the size and content of hemoglobin of the erythrocytes affects the reaction. Auto-agglutination has been suggested as influencing the reaction.

(*3*) *Surface tension, capillary attraction and differences in the electrical charges of the diverse elements of the blood* may influence the speed and degree of the sedimentation.

Little attempt has been made in the present clinical study to investigate the causative factors in the phenomenon, but certain of them are being taken up for future study.

In 75 cases complete blood counts were made on the patients tested, and little or no relationship could be demonstrated between the rate of sedimentation and the red, white or hemoglobin determinations.

CONCLUSIONS

1. There is a definite increase in the velocity of erythrocyte sedimentation in active pulmonary tuberculosis.

2. No constant relationship can be shown between the rate of sedimentation and the extent of pulmonary lesion, though rapid sedimentation will be found to occur in a far larger percentage of patients with extensive lesion than in those with slight lesion.

3. The test seems to offer a valuable estimation of the degree of activity. Patients with definite symptoms of activity, fever and rapid pulse, always give a rapid sedimentation while those patients who are judged to be quiescent usually give readings within normal limits, though to this latter statement there are not infrequent exceptions, especially in women.

4. The test has little value in the diagnosis of tuberculosis.

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THE DARANYI FLOCCULATION REACTION IN PULMONARY TUBERCULOSIS[1]

MAX PINNER

The large number of serum reactions advocated for the diagnosis of active tuberculosis may be grouped into three divisions. There is first, the group of antibody reactions, such as complement deviation, agglutination and precipitation. Recent reports show that none of these reactions is fully reliable for diagnosis.

The second group comprises the reactions which attempt to demonstrate the presence of specific antigens in the body. Wildbolz's autourine reaction is based on this principle. The principle is certainly very sound, but in its application one finds that the nonspecific constituents of the urine give rise to nonspecific reactions. In a series of about 100 cases examined by the Wildbolz test we were unable to obtain reliable diagnostic results. Hendrichsen and Sweany have shown that by using the patient's serum instead of his urine (Lanz) the results are more promising. Marmorek tried to demonstrate the presence of specific antigens in the blood by complement fixation, using a tuberculous antiserum. Recently Fried has published data along the same line, but he was unable to obtain satisfactory results.

The last group of reactions which have been propounded classify tuberculous cases as "active or nonactive." They are based on nonspecific alterations in the blood and do not attempt a specific diagnosis. Westergren believes the application of Fahraeus's sedimentation reaction to tuberculous patients differentiates active from nonactive cases. Numerous investigators (Linzenmeyer, Katz and Rabinowitsch, etc.) following his suggestion did not find the reaction to be fully reliable. In a series of 49 active cases I found 11 instances in which repeated tests gave invariably a normal sedimentation rate; 7 of the latter had positive sputum findings. These examinations did not substantiate the statement of Gräfe that active cases after injection of very small amounts of tuberculin show an increased sedimentation rate. Two of

[1]From the Laboratories of the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

the cases did not show an increase even during a rather severe systemic tuberculin reaction.

Daranyi (1) has recently described a test which he claims to be positive in every case of undoubtedly active tuberculosis. He calls his test "A reaction for the colloid-stability of the serum in cases of toxin-production in the organism." It is based on the fact that toxin-production and pathological tissue-destruction decrease the colloid stability of the serum. Daranyi does not give an adequate explanation of this phenomenon. In an attempt to explain the higher lability of tuberculous serum it is interesting to note that Sweany, Weathers and McCluskey have shown by chemical methods that the proteins as a whole increase slightly in tuberculosis and decrease in very advanced cases, and that the ratio of albumin to globulin is essentially changed. Alder arrived at similar conclusions, conducting his examination with refractrometric and viscosometric methods. The normal globulin ratio (according to Alder) is 20 to 35 per cent of the entire proteins, and increases in fair parallelism to the activity of the process to more than 80 per cent (see the similar studies by Frisch). It is well known that the globulins are the more labile constituents in the colloidal serum system. Thus these changes lend themselves readily as an explanation for the decreased stability of the tuberculous serum. Other blood changes which might be responsible for this phenomenon are the increase of fibrinogen and changes in the electrical charges of the plasma, which Hoeber has reported in his studies in the increased sedimentation rate of erythrocytes. Herzfeld and Klinger have observed an increase of the amount of protein cleavage products (amino-acids), that might play an active rôle in the Wassermann reaction (Much). It may be of interest to mention here that Karl Meyer found an increase of globulins not only in infectious diseases but also during the process of immunization with dead material.

Whatever the explanation might be, the fact is that by the threefold action of salt, alcohol and heat, as employed in the Daranyi test, tuberculous sera flocculate, whereas normal sera will remain undisturbed. Reasoning that "activity" in tuberculosis must mean toxin-production and tissue-waste, it is obvious how promising it would seem to use this test in order to distinguish active from nonactive cases. Of course, the test is not specific for tuberculosis. It is positive in all diseases which produce toxemia and tissue-destruction, such as active syphilis, malignant tumors, certain metabolic disturbances and certain

infectious diseases. It is the purpose of this paper to report the application of the Daranyi test to the diagnosis of activity in tuberculosis. The question as to the value of this reaction in prognosis will also be discussed.

LITERATURE

Daranyi (1) reports that in about 300 cases of active tuberculosis the test has always been positive. It has always been negative in healthy persons. The results of Baum and Schumann (2) are similar to Daranyi's, but they report three cases of pulmonary tuberculosis with positive sputum findings which gave negative results with the Daranyi reaction. For this reason they modified the reaction, using a larger amount of serum and alcohol and testing five different amounts of serum from each patient. They believe that this makes the reaction more sensitive, as with this modification they obtained positive results in the three cases mentioned above. Kuchen (3) states rightly that this modification, increasing the sensitiveness of the test, tends to positive reactions with normal serum. In an analysis of 300 cases Kuchen found in latent cases no positive reactions, in cases with "tendency to become latent" 20 per cent positive reactions, in cases with "tendency to progredience" 68 per cent positive, and in progressive cases 77 per cent positive. To demonstrate that the Daranyi reaction is more dependent on the pathological nature of the process than on its extension, this author gives a classification of active cases as follows: Sclerotic type, 40 per cent; acinous-nodular type, 58 per cent; and exudative-pneumonic type, 88 per cent positive. In 23 per cent of undoubtedly active and destructive cases, the test was negative.

Kremer (4) applied the test to tuberculosis and reports favorable results. He believes that it gives a valuable prognostic criterion if combined with the determination of the serum lipases. Baldassare Sardo (5) states that he found the test to be negative in all healthy individuals. It was positive in cases of broncho-alveolitis and weakly positive in one case of chlorotic anaemia and in one case of lymph-node tuberculosis. He believes that the reaction has considerable prognostic value, and stresses the importance of repeated tests. In a series of 100 examinations deJong, Wolff and Azerad (6) found 59 positive reactions in active tuberculosis, 3 in *asystoliques graves* and 1 in pulmonary cancer. They always obtained negative results in healthy individuals, in cases of quiescent tuberculosis and in some other dis-

eases. Like Kuchen, they had a few negative reactions in rather far-advanced tuberculous patients. The authors are of the opinion that this test is of no value in the diagnosis of tuberculosis, but may be of significance in prognosis. Owing to the altered colloid stability of the serum in the newborn, Duzar (7) had to adapt the alcohol concentration in order to conduct his examinations on tuberculous infants. He found a positive test, the strength of which was parallel to the severity of the process in all tuberculous infants. Healthy children gave negative results.

Kroemeke (8) applied the test to syphilitic cases, and states that this reaction indicates with sufficient accuracy the degree of systemic infection or the amount of toxin-production. Mendel (9) found the test positive in acute infections of children; slight infections gave varying results. In congenital syphilis he did not find any parallelism between the Daranyi test and the clinical findings or the Wassermann reaction. He does not consider the test to be applicable to prognosis. Nassau and Hendelsohn (10) found the test to be positive in certain nutritive disturbances in children.

METHODS AND RESULTS

The technique of the test as described by Daranyi is as follows: 0.2 cc. serum is mixed with 1.1 cc. diluted alcohol and kept in the water-bath at 60° for 20 minutes. The tubes are then removed and readings made ½, 1, 2, 3 and 24 hours after the time of their removal from the water-bath. A positive test shows a rather heavy and coarse flocculation, and a negative serum remains clear. A reaction which is positive after ½ or 1 hour is ++++; after 2 hours is +++; after 3 hours is ++; and after 24 hours is +. The alcohol is diluted with 2 per cent NaCl solution. The suitable concentration is found by titrating different alcohol dilutions against normal sera. The highest concentration of alcohol which gives a negative reaction with normal sera is used for the test. This is approximately a dilution of 1 cc. of 96 per cent alcohol plus 4 cc. of 2 per cent NaCl solution. Technical details may be found in Daranyi's original paper.

I used a slightly modified technique, taking two tubes for each serum. The first tube is the one described in Daranyi's technique. In the second tube I used a weaker alcohol dilution, thinking that a flocculation obtained in this tube would certainly indicate a high degree of

decreased stability, the purpose being to widen the range of the reaction toward the positive side. Readings were made ½, 1½, 2½, and 24 hours after the tubes were removed from the water-bath. I read the results by means of the Kuhn-Woithe agglutinoscope, which facilitates the distinction of negative and positive results. The question of the significance of an early flocculation in preference to a flocculation occurring in the second tube was studied, but no definite conclusion was obtained. Therefore, I would advocate the use of Daranyi's original technique, making the readings with the agglutinoscope.

TABLE 1

	ENTIRE NUMBER	POSITIVE	PER CENT POSITIVE	PER CENT NEGATIVE
1. Undoubtedly active tuberculous cases	368	328	89.1	10.9
a. Incipient	56	41	73.2	26.8
b. Moderately advanced	106	97	91.5	8.5
c. Far advanced	199	184	92.4	7.6
d. Pleurisy without lung involvement	4	4	100.0	0.0
e. Urogenital tuberculosis	3	2	66.6	33.3*
2. "Clinically arrested"	13	4	30.7	69.3
3. Glandular tuberculosis (mostly children)	68	17	25	75
4. "Suspect of tuberculosis"	40	28	70	30
5. Bronchiectasis, bronchial asthma, lung abscess, chronic empyema	15	12	80	20
6. Pulmonary carcinoma	1	1		
7. Normal individuals	5	0	0	100
8. Women shortly before or after confinement	18	6	25	75
9. Old malaria	1	1		
10. Severe secondary anaemia	2	2		

* The one negative case was a case of incipient tuberculosis of the bladder, with bacilli in the urine.

The test was applied to 534 patients, and in table 1 a classification is made of the different diseased conditions, according to the diagnoses received from the clinical department. The diagnoses "incipient," "moderately advanced" and "far advanced" are made chiefly on the strength of local findings, whereas the Daranyi test discloses alterations in the colloidal serum system as the result of the local process in the lung. It is obvious that merely for this reason one cannot expect an absolute agreement between the clinical findings and this test. The diseased condition that a positive Daranyi test indicates is different from the condition the clinician looks for in order to form his diagnosis. But any laboratory procedure must prove its value for the clinician by comparison of its results with clinical findings.

An analysis of table 1 shows that from a diagnostic point of view the test does not fulfil the promises that Daranyi has given. It was negative in 10.9 per cent of undoubtedly active cases. More important, it was negative in 26.8 per cent of incipient active cases. In 18 incipient cases with positive sputum findings 2 gave a negative test, and in 37 incipient cases without bacilli in the sputum 12 gave a negative test. In these cases we must suppose that the action of the infection on the serum has not been severe enough to bring about the alterations demonstrable by Daranyi's methods.

Even in the group of far advanced cases we find 7.6 per cent of negative reactions, and Kuchen's figure is as high as 23 per cent. The explanation advanced for the negative results in incipient cases is obviously not valid for the far advanced cases. Most of the negative tests in far advanced cases are found in patients *in extremis*. This occurrence might be explained by the decrease of the entire proteins in the very far advanced cases (Sweany, Weathers and McCluskey, Alder).

In four cases of exudative pleurisy, without any apparent lung involvement, I found two 4+, one 3+, and one 1+ reaction, which is a rather significant finding, as exudative pleurisy is an acute and active manifestation of tuberculosis.

The group of urogenital tuberculosis is far too small to draw any conclusions.

The term "clinically arrested" means only that the temperature is normal and stays normal, even after a certain amount of exercise, that no râles can be heard, etc. This group includes some cases with bacilli in the sputum. Most probably, the 30 per cent of positives belong, on the strength of the positive Daranyi reaction, to the group of active cases.

Whether a case of lymph-node tuberculosis is active or not can hardly be decided by clinical examination alone, unless definite symptoms of activity, such as fever or pus-formation, be present. Observation over a period of years will have to decide how significant the Daranyi test is in regard to this type of case.

The cases under "suspect" are patients who show suggestive but not conclusive signs of tuberculosis, or cases of children who have been in contact with bacilli-carriers. This group can obviously not be used for the valuation of any test.

It is important to note that no healthy person was examined who gave a positive test. The only exceptions are women shortly before or after confinement; the physiological processes give ample explanation for this finding. In these cases the test was weakly positive. The blood of the newborn normally is much more labile than in the adult (Sachs and Öttingen); this accounts for a positive test that I had with the cord-blood of a healthy infant. If the Daranyi test is to be applied to examinations of infants, it is necessary to titrate the alcohol against the blood of normal infants, as mentioned by Duzar.

The rest of the table shows a few other diseases in which the test has been found to be positive. Aside from the cases reported in table 1, the test was negative in one case of laryngeal syphilis, in one case of whooping cough, and in one case of chronic bronchitis.

TABLE 2

	INCIPIENT	MODERATELY ADVANCED	FAR ADVANCED
	per cent	*per cent*	*per cent*
Reaction+	40	21	8
Reaction++	22	29	22
Reaction+++	15	18	25
Reaction++++	22	32	45

Has the strength of the reaction any bearing on the nature of the case? In table 2, 266 cases of active pulmonary tuberculosis are grouped according to the strength of the Daranyi reaction.

This table shows less regularity than one might expect, although there are very definite differences among the three groups, especially if one considers only the 1+ and 4+ reactions, with 40, 21, and 8 per cent, and 22, 32, and 45 per cent, respectively. But here again the test would have a fairer showing if the cases were diagnosed according to the pathologico-physiological nature of the process, rather than according to its extension.

It is interesting to note the complete irregularity of group 2. The assignment of cases to this group includes certainly more discretion on the part of the clinician than is the case with group 1 or 3. The table shows that the test has only a limited application to prognosis. Repeated tests, however, are rather significant prognostically. A far-advanced case which quiets down after a long period of rest is still listed as a far-advanced case. Invariably such a case will give a nega-

tive or only weakly positive test. In this point the true value of the test spoils its statistical presentation. In a group of 90 far-advanced positive Daranyi cases, which included only patients which were very recently admitted to the Sanitarium, only 3 per cent had a 1+ reaction, and only 12 per cent a 2+ reaction.

In a detailed study of about 70 cases, in which the Daranyi was applied and which I had the privilege to examine clinically over a period of several months, the conclusion was drawn that any tuberculous patient who has a positive Daranyi test (2+ or more) should be at rest, no matter what his physical findings may be, provided, of course, that no other pathological condition exists which may be responsible for the positive test. A third-stage case after a long period of rest, and with a negative Daranyi test, is more in a condition of equilibrium, than an incipient case with a much disturbed colloidal structure.

SUMMARY AND CONCLUSION

1. The technique of the Daranyi test as applied to 534 patients is reported.

2. The test is of little diagnostic value in tuberculosis, but it appears to be a sensitive indicator for alterations in the colloidal stability of the serum in diseased conditions, and it gives valuable information as to the severity of the destructive process.

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SERUM PRECIPITATION FINDINGS IN ACTIVE TUBERCULOSIS[1]

FELIX BAUM

To determine whether a case of tuberculosis is active or not, numerous attempts have been made by immunologists (Sachs, Oettingen, Daranyi, Wassermann, Matefy and others) to solve the problem by serological methods, which in many cases are complicated and time-consuming. Sachs and Oettingen (1) especially call attention to the importance of the changes in the colloids of the blood under certain conditions. Levinson (2), in studying the toxicity of human blood plasma for guinea pigs, found that the toxicity in pulmonary tuberculosis is increased for the guinea pig, while the suspension stability of the blood in pulmonary tuberculosis parallels the activity of the process. With an increase in the pulse rate and temperature there is also an increase in the sedimentation rate of erythrocytes. The pulse, temperature, suspension stability of erythrocytes, and toxicity of the blood plasma run parallel.

That there is a colloid instability of the blood serum in cases in which there is a destruction of tissues (especially in active cases of tuberculosis) seems fairly well established, but most tests for determining this are elaborate and time-consuming. In view of these facts a simple rapid method has been utilized for the past two years (3) for determining the colloid instability of the blood of tuberculous animals and human beings. The method in brief is as follows:

A. A dilute solution of alcohol is daily prepared for use by mixing 10 cc. of ethyl alcohol (exactly 96 per cent) and 41 cc. of 2 per cent sodium-chloride solution.

B. Into five small test tubes 7 cm. long and 1 cm. in diameter are placed:

in tube 1: 0.5 cc. clear blood serum;
in tube 2: 0.4 cc. clear blood serum;
in tube 3: 0.2 cc. clear blood serum;
in tube 4: 0.1 cc. clear blood serum;
in tube 5: 0.08 cc. clear blood serum;

The serums must be tested before 24 hours have elapsed after withdrawal of the blood from the vein.

C. To each tube, 1 to 5, is added 2.75 cc. of solution *A*. The tube is closed with a rubber stopper and rotated carefully three times.

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[1] From the National Jewish Hospital for Consumptives, Denver, Colorado.

D. All the tubes are then placed in a 60°C. water-bath for 30 minutes, after which they are kept at room temperature, and are then read after 4 and 24 hours.

A flocculent precipitate in tubes 4 or 5 indicates a strongly positive or ++++ reaction.

A flocculent precipitate in tube 3 indicates a medium or ++ reaction; and a flocculent precipitate in tubes 1 or 2 indicates a weakly positive or + reaction.

Since there are serums which occasionally give a negative reaction at 4 hours, becoming strongly positive at 24 hours, all tubes examined earlier than 24 hours should again be reëxamined at this time. In questionable cases it may also be necessary to centrifugate the tubes after 48 hours in order not to miss a possible positive reaction. Later than this readings should never be made. The serum to be tested must be free from corpuscles or hemoglobin, and must not be inactivated by heat, to avoid erroneous results. A flocculent precipitate (not to be confused with the homogeneous opalescence seen in the negative tubes: see fig. 1) in tubes 3, 4, and 5 indicates an active tuberculosis in the case from which the serum was obtained, while a negative reaction, or absence of a flocculent precipitate, in all the tubes indicates an absence of activity.

A positive reaction in tube 1 or 2 (faintly positive) is seen, though rarely, in certain nontuberculous cases, such as acute tonsillitis, nontuberculous bronchitis, nephritis, pregnancy, etc.

In this study the serums from 246 individuals were examined, including 233 human beings, 11 monkeys and 2 dogs. Of the 233 human beings studied, 162 had active clinical symptoms of tuberculosis, 49 were suspiciously tuberculous, 2 had pertussis, 1 had a pulmonary (nontuberculous) tumor, 1 had nephritis, and 5 were normal pregnant women. Of the animals examined, 2 monkeys had spontaneous tuberculosis, while 9 monkeys and 2 dogs had generalized tuberculosis produced by the intravenous injection of virulent human tubercle bacilli.

The summarized serological findings were as follows:

(1) All exudative, ulcerative (cavity), miliary and caseous pneumonic cases gave a strongly positive reaction.

(2) Fibroid cases gave a moderately positive reaction.

(3) Early cases, hilum tuberculosis and a few nontuberculous cases gave a faintly positive reaction.

(4) All the monkeys and one dog gave strongly positive reactions. These animals (except 2 monkeys with spontaneous tuberculosis) all had a miliary hematogenous tuberculosis. One dog with a mild nodular tuberculosis in the lungs gave a faint positive reaction.

FIG. 1

Tube 1. A negative reaction. There is a homogeneous opalescent appearance of the test liquid which gives no sediment after centrifugation at high speed.

Tube 2. A positive reaction. There is a white flocculent precipitate which adheres to the wall of the test-tube and slowly settles out, leaving a clear supernatant liquid.

Tube 3. A positive reaction after centrifugation. There results a compact sediment under a clear supernatant liquid.

Among the human cases there were several selected to be reported below which proved of special interest:

1. Case 121: A merchant, 48 years of age, ran subfebrile temperature, had a cough and dyspnea for 8 months. The consultant roentgenologist made the following diagnosis: Progressive exudative tuberculosis, Turban III, of both lungs. The sputum on numerous examinations was always negative for tubercle bacilli. A clinical diagnosis of tuberculosis or pulmonary tumor (?) was made. The sero-diagnosis by the above method turned out negative. At autopsy there was found a diffuse metastatic tumor of both lungs with the primary focus in the left suprarenal gland.

2. Case 164: A child, 7 years of age, ran a temperature between 98 and 100°F. during 4 weeks prior to testing the serum. The mother of the child was at the same time being treated as a fibroid open case of pulmonary tuberculosis. The X-ray examination of the child's chest revealed a considerable enlargement of the glands of the hilum on both sides. The Pirquet test and D'Espine sign were both positive. The clinical diagnosis was suspected tuberculosis of the hilum glands. The sero-diagnosis test was medium reaction after 4 hours, and strongly positive at 24 hours. During the 3 months subsequent to the sero-diagnosis test the child developed a progressive exudative tuberculosis of the upper lobe of the right lung and was given artificial-pneumothorax treatment.

3. Case 13: A girl, 18 years of age, developed influenza in December, 1922, and was confined to bed for 3 weeks. Since then she has been running a temperature ranging from 99 to 99.8°F. There was a loss of appetite, loss of weight and a general weakness. On February 16, 1923, sputum examination revealed only pneumococci, and tubercle bacilli have never been found in the sputum. Physical examination revealed dulness over the right apex and the presence of suspicious râles. X-ray examination revealed considerable involvement of the upper lobe of the right lung, and the hilum shadows on the right side were enlarged. The sero-diagnosis test turned out negative. On June 3, 1923, a second X-ray examination was made, and showed the right apex to be entirely clear and the hilum shadow on the right side much diminished. The clinical findings at this time included an absence of dulness and râles. The patient's general condition is good at present, and the final diagnosis made was a protracted influenza with resolution of the pulmonary infiltration. No tuberculosis.

4. Monkey D (Macacus Rhesus): Received from an Eastern animal dealer, the animals just arrived from India and never having been infected. The sero-diagnosis test turned out strongly positive, and at postmortem there was found an isolated tuberculous abscess in the left lung.

5. Monkey A (Macacus Rhesus): Infected by intravenous inoculation of virulent human tubercle bacilli. After 2 weeks the sero-diagnosis test was strongly positive and at postmortem there was found a miliary tuberculosis of all the organs.

6. Case 147: A male, 26 years of age, had cough, fever, headache and general malaise of several weeks' duration. The X-ray findings revealed small suspicious shadows in the left apex. The rest of the lungs appeared normal. The consulting roentgenologist's diagnosis was questionable early tuberculosis of the left apex. The sero-diagnosis test turned out negative. Subsequent clinical observation verified the fact that the patient was free from tuberculosis.

SUMMARY AND CONCLUSIONS

In conjunction with clinical findings the graded sero-diagnostic alcohol sodium-chloride precipitation test has proved of practical value. A medium or strongly positive reaction was never obtained in a non-

tuberculous human being. Cases of active tuberculosis in every case examined gave a positive sero-diagnostic reaction, ranging from faintly positive to strongly positive, depending upon the grade of activity of the case in question. The sero-diagnostic alcohol sodium chloride precipitation test is not specific for tuberculosis, since a positive test may be obtained in other diseases and abnormal conditions, but in conjunction with accurate clinical data it is an easily performed adjunct to our present methods of examination for tuberculosis and especially for the presence of activity in tuberculous individuals. Its value seems to be in the differential diagnosis of doubtful cases of tuberculosis, in addition to determining the state of activity in tuberculosis.

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THE LOCAL EFFECT OF ALCOHOL ON EXPERIMENTAL TUBERCULOSIS[1]

MAX GOLDBERG AND MILTON B. LORBER

It seems fairly well established that ethyl alcohol, on systemic administration, has no direct beneficial effect on pulmonary tuberculosis, yet every now and then there appear a few who enthusiastically advocate its local use, with apparent justification, in surgical tuberculosis (1). The natural question arises of whether the alleged favorable action is due to a mere cleansing property of the alcohol, to its chemotactic property (2), or to the alcohol entering the tissues in concentration sufficient to destroy the tubercle bacilli. It appears that the bactericidal action of ethyl alcohol is most pronounced at concentrations of from 60 to 80 per cent, a maximum effect occurring at 70 per cent (3), concentrations at which serum proteins are most efficiently coagulated by the alcohol (4). If this also applies to the tubercle bacillus (which apparently has not been previously tested in this way), it would seem that alcohol applied locally cannot act as a tuberculocide in the tissues on account of its tissue-coagulating and necrosing effects and the fact that the bacilli are localized in the tissues themselves. There still remains then the possibility of a chemotactic influence of the alcohol with a consequent indirect effect upon the disease, and this can only be determined by controlled animal tests.

Although the clinical literature contains numerous references, pro and con, to the benefits derived from the use of alcohol in tuberculosis in man, that on the effect of alcohol on tuberculosis in animals consists of a few brief articles.

There is some intimation in the experimental literature (5) that after general administration and in proper small dosage alcohol has an antitoxic effect, but, because of our present knowledge regarding immunity in tuberculosis and especially because our interest in this study lies in its local effect, this view need not be considered here. Gervino (6), from a rather indecisive experiment with four rabbits, concluded that

[1] From the Research Department, National Jewish Hospital for Consumptives, Denver, Colorado.

the administration of wine to the animals favored resistance to tuberculosis. Roos (7) gave a large series of tuberculous guinea pigs wine, and found that the alcohol in this form did not aggravate or modify the course of infection in these animals.

Achard and Gaillard (8) divided 60 guinea pigs, given intrapleural injections of human tubercle bacilli, into three lots of 20 each. One lot served as controls; the second received subcutaneous injections of alcohol; and the third, the same amount of alcohol by mouth three times a week. The controls far outlived the animals receiving the alcohol. Forty other guinea pigs were likewise infected intrapleurally with human tubercle bacilli, and one-half were given daily inhalations of alcohol vapor, beginning 14 days prior to infection. The control animals outlived those given alcohol inhalations. It was concluded that alcohol intoxication hastened the course of experimental tuberculosis. Laitinens (9) in 1911 also found that alcohol had a harmful influence upon tuberculous rabbits and guinea pigs and their offspring.

It was the purpose of the following study to determine whether alcohol, in concentration producing at most only a transient tissue injury, would have any influence on the course of tuberculosis in guinea pigs. Since the guinea pig is a highly susceptible animal to tuberculosis, the local and general tuberculous involvement at definite intervals after infection, in control and treated animals, would serve to indicate the local effects of the alcohol (10) (11).

As a preliminary measure the general and local toxicity of the ethyl alcohol used throughout these experiments was tested in rats and guinea pigs. In full grown white rats 10 cc. of 70 per cent alcohol, given subcutaneously, resulted fatally in 2.5 hours, while 7 cc. produced, besides the immediate symptoms of acute alcoholism, profound local tissue-destructive effects with recovery; 1 and 5 cc. also resulted in recovery with slight local tissue-destructive effects. In the guinea pigs, the immediate results of the subcutaneous injection of the 70 per cent alcohol were about the same as in the rats; 10 and 20 cc. proved lethal while 5 cc. resulted only in local tissue-destructive manifestations. In guinea pigs 10 and 20 cc. of 50 per cent alcohol proved lethal in about 6 hours, with local hemorrhage and edema; while 5 cc. was tolerated without death, and produced profound local tissue changes with hemorrhages and edema.

In guinea pigs, 5, 10 and 20 cc. of 20 per cent alcohol produced slight tissue changes, bordered by a narrow band of hyperemia, which, how-

ever, gradually subsided. In spite of the fact that all concentrations of alcohol from 20 to 70 per cent, injected subcutaneously, had an injurious effect upon the tissues (that occurring with 20 per cent was transient in character), surface compresses of 70 per cent alcohol applied to the skin were fairly well tolerated without perceptible injury. In order to test the effect of the alcohol in different concentrations on tubercle bacilli, dilutions of 10, 20, 40 and 60 per cent in sterile 0.9 per cent sodium-chloride solutions were made, and to each tube containing the different dilutions of alcohol was added a fine suspension of virulent human tubercle bacilli, capable of infecting guinea pigs in a dose of less than 0.000,001 mgm., so that each 0.1 cc. of solution contained 0.01 mgm. of bacilli. The tubes containing the suspended bacilli in alcohol and saline controls were incubated for two hours, after which a series of guinea pigs was injected with 0.1 cc. from the different tubes. The guinea pigs were then examined postmortem two months later with the following results:

The tubercle bacilli kept for 2 hours at incubator temperature in 40 and 60 per cent alcohol did not produce tuberculosis in the guinea pigs within 2 months, while the bacilli in the 20 per cent alcohol for 2 hours produced a slight but definite tuberculosis in the two guinea pigs examined 2 months after injection. Exposure for 2 hours at incubator temperature to 10 per cent alcohol had no appreciable effect upon the tubercle bacilli, since the two guinea pigs receiving these injections developed a marked generalized tuberculosis within 2 months, that was equal to that seen in the control guinea pigs that had received the bacilli suspended in 0.9 per cent sodium-chloride solution for 2 hours at incubator temperature. It was thus evident that 40 per cent alcohol for 2 hours at incubator temperature had killed all the tubercle bacilli while 20 per cent was incapable of destroying all of them.

Thus far the experiments seemed rather encouraging but the final *in vivo* animal tests did not prove so fruitful. A series of guinea pigs was given intracutaneous injections of different amounts (0.1, 0.000,01 and 0.000,000,01 mgm.) of virulent human tubercle bacilli, and some of the animals were treated by injecting locally at daily intervals 30 per cent ethyl alcohol, while others were treated by the daily local application of compresses of 70 per cent alcohol, and some of the guinea pigs were kept as controls untreated. The local intracutaneous site, the local lymph nodes and the general involvement at postmortem 6 to 8 weeks afterward were noted with the results recorded in table 1.

TABLE 1

The effect of the local subcutaneous injection and local cutaneous application of ethyl alcohol on tuberculosis in guinea pigs

ALCOHOL TREATMENT ACCORDED ANIMAL	ANIMAL	INFECTING DOSE OF VIRULENT HUMAN TUBERCLE BACILLI INJECTED INTRACUTANEOUSLY								
		0.1 mgm.			0.000,01 mgm.			0.000,000,01 mgm.		
		Local intracutaneous site	Local lymph nodes	General tuberculous involvement	Local intracutaneous site	Local lymph nodes	General tuberculous involvement	Local intracutaneous site	Local lymph nodes	General tuberculous involvement
Alcohol (30 per cent) injected immediately after infection and on 3 succeeding days thereafter	1	U*	++†	+++‡	Died 9 days			Died 12 days		
	2	0	+	++	0	++	+++	0	+	++
Alcohol (30 per cent) injected on the 1st day after infection and on 3 succeeding days thereafter	3	0	++	+++	Died 7 days			0	++	++
	4	0	++	+++	0	++	++	0	+	+
Alcohol (30 per cent) injected on the 2nd day after infection and on 3 succeeding days thereafter	5		Died 5 days		0	++	+	0	0	0
	6	0	++	+++	Died 8 days			U	++	++
Alcohol (30 per cent) injected on the 4th day after infection and on 3 succeeding days thereafter	7	U	+	+++	0	+	+	0	+	++
	8	0	++	+++	Died 10 days			U	++	++
Alcohol (30 per cent) injected on the 8th day after infection and on 3 succeeding days thereafter	9	0	++	+++	0	++	++	0	+	+
	10		Died 15 days		U	++	+++	0	++	+
Local application of 70 per cent alcohol compresses for 3 weeks	11	0	+	+++	0	+	++	0	+	+
	12	0	+	+++	0	++	+++	0	+	+
Controls not treated with alcohol	13	0	+	+++	0	++	++	0	+	++
	14	0	++	+++	0	+	+++	0	+	+

* "U" in the column under "local intracutaneous site" indicates that an ulcer developed at or near the site of injection of the tubercle bacilli, either as a result of the alcohol treatment or the local action of the bacilli. If no ulcer but a nodular tubercle developed locally it is marked "0". In the 0.1 mgm. dose a nodule developed in each case locally.

† The enlargement of the local lymph nodes is graded as follows: 0 = no appreciable enlargement, + = a moderate distinct enlargement and ++ = a pronounced enlargement.

‡ The general tuberculous involvement of the animal is graded from 0 = no visible internal involvement, + = a distinct involvement of the internal lymph nodes and the spleen, ++ = an involvement of the internal lymph nodes, the spleen, lung and liver, to +++ = a massive involvement of all the internal organs.

An examination of table 1 seems to indicate that neither the local injection of 30 per cent alcohol around the site of the intracutaneous inoculation of virulent human tubercle bacilli nor the local application of compresses of 70 per cent ethyl alcohol over the site of the intracutaneous inoculation of the tubercle bacilli has an appreciable effect on the development of the local tuberculous lesion in these animals nor on the systemic spread of the disease from the local intracutaneous site of injection. The beneficial effect seen clinically must, therefore, be attributed to such cleansing properties as ethyl alcohol may possess in common with many other substances.

SUMMARY

Ethyl alcohol, in concentration (30 per cent) not capable of producing profound local tissue changes upon injection around a local intracutaneous site of infection with virulent human tubercle bacilli, has no appreciable effect on the development of the local tuberculous lesion, the local lymph-node involvement or the systemic disease. Likewise, compresses of 70 per cent ethyl alcohol, locally applied to an intracutaneous site of infection with tubercle bacilli in guinea pigs, has no influence on the tuberculosis developing subsequently. Concentrations of ethyl alcohol as low as 20 per cent in physiological saline solution have a detrimental influence on virulent human tubercle bacilli when the bacilli are suspended therein for 2 hours at incubator temperature, while 10 per cent alcohol is without effect.

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A REPORT OF A CONFERENCE[1] ON THE CHEMICAL RESEARCHES NOW BEING CONDUCTED ON GRANTS FROM THE NATIONAL TUBERCULOSIS ASSOCIATION[1]

The meeting was called to order at 10:35 A.M. by the Chairman, Dr. William Charles White, at the Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia, Pa.

Those present were Drs. William Charles White, Washington, D. C.; Paul A. Lewis, of the Rockefeller Institute, Princeton, N. J.; Allen K. Krause, Baltimore, Md. (Johns Hopkins University); Treat B. Johnson, New Haven, Conn. (Yale University); Esmond R. Long, Chicago, Ill. (Sprague Institute); Hans Zinsser, Boston, Mass. (Harvard University); Eugene L. Opie, Philadelphia, Pa. (Phipps Institute); John J. Abel, Baltimore, Md. (Johns Hopkins University); H. R. M. Landis, Philadelphia, Pa. (Phipps Institute); Linsly R. Williams, New York City (Managing Director of the National Tuberculosis Association); Alfred N. Richards, Philadelphia, Pa. (University of Pennsylvania); Charles J. Hatfield, Philadelphia, Pa. (Phipps Institute).

DR. WHITE: I want, on behalf of the Committee, to thank you who have given your time to come here and help The National Tuberculosis Association in its endeavor to outline a safe program in the new field of research work which it has undertaken in the last few years in order to secure more accurate knowledge on the question of tuberculosis, which is undoubtedly the biggest single economic factor with which the country has to deal from the standpoint of health. The evolution of the work has been rather slow and quiet, but it has been a necessity long apparent to the Committee, and fundamental in importance, that in all work undertaken in this field there be a uniform agreement of those who are competent to judge as to the theories that offer the best avenues to be followed in endeavoring to solve this question. It is quite true that the tubercle bacillus has the most voluminous literature that has

[1] Called by the Medical Research Committee of the National Tuberculosis Association, March 7, 1924.

ever been contributed on a single microörganism of disease; yet this field is probably the most hazy of all as to what avenues of attack are sound and most likely to bring a solution.

The Committee, composed of Dr. Lewis, Dr. Krause, Dr. Hatfield, Dr. Williams and myself, has found a great deal of perplexity in dealing with the question, but all the members were convinced at the beginning that the chemical side of the problem was the most important while the most intricate to solve. It involved not only the chemistry of the bacillus itself, but the chemistry of the host, which while of the same type is more complex. It finds itself still in some doubt; and has therefore decided to ask a representative from four different divisions of chemical research to confer with it and to let the Research Fellows who have been working under the National Association present their subjects in a way that has been written to each member of the conference. That we may all start on a uniform basis one member of the Committee, Dr. Lewis, has undertaken to outline the subject of Tuberculosis Research as it exists in our mind at the present time; and I will ask now Dr. Lewis to say a few words on this subject; and if there are variations in the minds of the members here that should be added to it Dr. Lewis will be glad to follow the discussion which takes place on the present situation of the Tuberculosis Research Problem with a purpose to include these suggestions in his statement.

DR. LEWIS: Gentlemen: I think the title as announced by Dr. White and sent out on the program may have given the conference a somewhat false impression of my function as I conceive it. I certainly have no intention of touching the chemical aspects of the tuberculosis problem technically. I am not competent to do so. But it does seem that in starting a day's discussion on one phase of so large a problem it might be an advantage to have a brief general statement of those aspects of the whole concerning which we may all be presumed to agree, so that we may start from a common standpoint, and this, in a few words, I have undertaken to give. I hope there will be no need for discussion because if I am successful I hope to state those things which I do state in such a way that they will be tacitly agreed to. The more definitely what I say meets with the agreement of all, the better I shall be satisfied. On the other hand, it is perfectly clear that there should be so much discussion of this phase of the question as will lead to a perfect understanding on the part of all concerned before we start the more serious subject of the day.

Tuberculosis is an infectious disease. It is caused by a particular bacillus very well known by workers of bacteriology and pathology, and well known in certain of its aspects to many chemists. The tubercle bacillus exists in three main types, namely, human, bovine, and avian, corresponding generally to the species infected, but cross infections are well recognized. Tuberculosis is a chronic febrile disease; it has peculiar features which enable it to be recognized fairly well as contrasted with other infectious diseases, either clinically or at the post-mortem table. There has been a great deal of controversy about how this disease comes to exist in the body, that is, what are the paths of infection. There is no question about the actual sources of infection; it is transmitted from an animal or man in which the disease exists to another animal or man in which it does not exist; but the paths of infection have been subject to a great deal of discussion and dispute. I do not think we need be concerned with this further than to say that probably the more bizarre explanations as to how this comes to be would to-day be considered as incidental: and it may be agreed that in the majority of cases of pulmonary tuberculosis infection is primarily by the way of the respiratory tract; that it may localize in the respiratory tract after other modes of introduction; that intestinal forms do exist; that they may extend; that it may be possible in the end to trace in an individual animal, in some but not all instances, the course by which the particular infection took place. The question of infection has also been the subject of much controversy from another point of view, namely, whether all infection takes place at a particular period of life, most notably in early childhood; and then so operates that superimposed, subsequent infections do not take place, or cannot take place, or are not required to take place, in order to account for all the phenomena of the disease. Or whether, on the other hand, granted that many people are infected in early life, there are superadded infections later in life which account for the phenomena of the disease as they are most apparent. I should assume that no one would presume, or could be presumed to be very dogmatic on this particular phase of the question; or that it would not be granted that infection does very frequently take place in childhood; that most would agree that infection may take place later in life whether or not infection has occurred in childhood; but that how it develops as a common phenomenon is a matter of uncertainty, the quantitative relationships not having as yet been sufficiently determined, and that probably only a much more careful study of all the phenomena of the

natural history of the disease, tuberculosis, on the basis of scrutiny of a large number of individuals, over a long period of time, by all methods at command, will really bring a decision. It may also be agreed that the more or less arbitrary methods of decision in the past have satisfied one that the actual decision cannot be reached on the basis of knowledge at present available.

It is certain from knowledge and experience that tuberculosis can from a theoretical standpoint be absolutely prevented; it can be prevented by keeping uninfected individuals out of contact with the bacillus and this has been demonstrated in the most clear-cut fashion in the Philadelphia Zoological Garden, the result being reported by Fox. Their monkeys have been for years quite free from tuberculosis and certain segregated stocks have been entirely free. The question as to whether it would be desirable to so prevent tuberculosis in the human race, considered as a racial question and over a long period of time, is doubtless academic, but it is one which does excite a good deal of interest; it has been rather frequently the subject of mild debate about this table between men like Dr. Biggs and Dr. Theobald Smith. Whether a certain amount of infection is desirable in order to keep up a degree of racial immunity is the question more directly stated and no one can give an answer to-day. We do know that from the individual's standpoint it is highly desirable to prevent infection if possible.

I think we are all agreed that there is such a thing as acquired or artificial immunity in tuberculosis. This can be established by injecting cattle with living human tubercle bacilli which are of a low grade of virulence for that species and it is effective at least up to a certain point; sufficiently so as to be perfectly convincing as to the fact of acquired immunity. This immunity seems to be what the Germans call *Infektionsimmunität*, that is, the living organism must be present in the body in order to make the immunity effective. When the bacteria die the immunity becomes very much less or completely disappears.

Whether the same result in active immunity may be accomplished eventually by the use of the dead organism, or any substance derived from it, or by any modification of the method of its administration is, I think, in the minds of all, one of the pressing problems with which we are faced and one along which no certain advance has been made.

Involved in this question is also the question as to the place of tuberculin as one of the constituents of the dead, and probably of the living, tubercle bacillus. There is no doubt whatever that certain phenomena

can be induced in the infected animal by the injection of tuberculin. This fact has been over-frequently rediscovered in many different forms. But it is probable that we should agree that we have not advanced greatly in our intimate knowledge of the subject over the rather simple manner in which it was put forward by Koch, as a question of local hypersensitiveness to the action of a presumed single extractive substance from the tubercle bacillus.

It is agreed, I think, by all that antibodies can be produced against the tubercle bacillus and its products, under certain special conditions, but it would be quite impossible to agree to any statement as to the place of these antibodies in the actual state of immunity as established by the injection of a living germ any more than it would be agreed by all just what the place of hypersensitiveness, as evidenced by the tuberculin reaction, should be in our conception of the mechanism of that immunity.

It is very well known, in fact it is one of the characteristics of the disease, that when the bacillus gains access to the mammalian body the tissues react in a certain way and the rather peculiar histological structure known as the tubercle is regularly produced. This involves a certain succession of cellular rearrangements, a complex which is well known to all pathologists. The function of the particular cells, or the dynamic factors in the succession of cellular rearrangements, is not understood. Certain studies have been made which indicate that the cells which are involved, or which may be involved, have quite different cytogenetic and tinctorial qualities from cells not so frequently involved. Dr. Opie's studies were fundamental in this direction and that line of research has continued up to the present time; and yet, I think, no one would consider that we really had facts of clearest significance developed in this connection.

We know that the dead tubercle bacillus and certain foreign bodies produce similar histological reactions, and yet differences arise at a certain point. Exactly wherein these differences consist would be a subject on which decision could not to-day be rendered. It would doubtless be agreed that the tubercle once formed can under certain circumstances be completely resolved. This is true even when there is a certain amount of caseation within the tubercle considered as an individual unit, but it would probably be impossible to decide in what measure this actually takes place, or what influence brought it about. Particularly is it uncertain how far large masses of caseous material

may be absorbed. It is clear that in connection with tubercle formation or resolution there frequently occurs calcification, but whether this is an active influence in the resolution or, in other words, in the healing of these tubercles, or whether it is a mere secondary deposit in altered tissues I think it would be difficult to decide.

It is perfectly clear from our general knowledge of the disease that the nutritional state of the body has a very pronounced influence on the question of the existence and the progress of this disease in the body. The results in Belgium and other occupied areas in Europe, which Dr. Williams is much more familiar with than I am, show in the clearest sort of way that this influence, whatever it may be, presumably exerted through nutritional states, is much more important and much more immediate in its action than one might have supposed. That is, an alteration for the worse in the economic state is very definitely and quite promptly marked out by the progress of tuberculosis in individuals or in communities. Whether the reverse effect is so rapid or effective would probably be very difficult to determine and how the effect of nutrition actually exerts itself in the case of an individual is, I take it, quite unknown.

A great question which has always been debated in connection with tuberculosis is the status of the individual's inheritance, his relation to the racial stock, whether individuals are uniform in their susceptibility, and it is possible that most people would agree to-day that there is some influence exerted through the race, but as to just how this is exerted there could be no hope of agreement.

Further, there is a word which is of intense interest to any discussion of the chemistry of tuberculosis or, in fact, of any other infectious disease to-day, namely, chemotherapy. It is doubtless to be agreed that from the experimental point of view, perhaps even as a matter of fundamental conception, this subject is still on a purely empirical basis. The interest which it may have for this gathering lies in the suggestion that the fundamental idea should always be in mind, and that those who have materials, possibly suitable, should not neglect even on a purely empirical basis to determine experimentally the therapeutic or preventive effect of them.

Now it is quite possible that I may have overlooked phases of the question about which all could agree and which we would all agree are important. I shall be very glad to have these called to my attention, and I shall be very glad to help, as Dr. White suggested, in the application

of any of the general matters I have touched on to the subjects of more immediate interest to this conference. I hope and expect that the discussion of the chemistry will be illuminating for many phases of the general biological problem.

DR. WHITE: I should like again to put as clearly as I can before the Committee the direct object of this conference, and that is that we should reach a program on which we are all agreed as to the most fruitful lines of study. Dr. Lewis has presented the subject as it appears at the present time with the emphasis on the closed door, or the problems which have to be solved, and I should like now, if you will, to undertake the discussion of that question, either subtracting from Dr. Lewis's statement, or adding to it, so that we get a basis from which we can all start in the discussion which will follow. Dr. Opie, have you any suggestions to make on Dr. Lewis's statement?

DR. OPIE: Dr. Lewis has presented the facts upon which I feel sure we can all agree and in listening to him I noted a few points upon which there is as yet no agreement. For example, we have no clear understanding of the significance of the tubercle which represents the reaction of the host to the parasite. The character of the cells which form it are well known, but we have no definite knowledge concerning the function which any one of these cells performs in the destruction of the tubercle bacillus. Knowledge concerning immunity is equally vague. What distinguishes the reaction of the host to the living bacillus from that which occurs when the dead bacillus or its products is introduced into the body? This question has no little significance in the search to find something which might increase resistance. A very large proportion of all adults exhibit a skin reaction to tuberculin, yet we are ignorant of its significance in relation to resistance. Dr. Lewis has discussed the question of racial resistance. We do not know whether racial resistance depends on natural or acquired immunity. These are a few of the many deficiencies in our knowledge of tuberculosis.

DR. WHITE: Dr. Zinsser, will you speak now, or would you prefer to speak later?

DR. ZINSSER: I think I would prefer to postpone anything I have to say until I have heard the greater elaboration of the chemical side. There are a great many things that occur to one, but I think perhaps a great many will be answered before the morning is over. If not, I shall be very glad to speak later.

DR. WHITE: Has anyone else any suggestions to offer at this time, or would it be your wish to go ahead with the chemical papers? If there is no objection we will proceed with the chemical papers. At the beginning of this work a proposition which Dr. Long offered in a paper on work which he had been carrying out at Saranac Lake, on the way in which the tubercle bacillus takes its nitrogen from various synthetic compounds, with only one way of securing nitrogen from each compound furnished, impressed the Committee as a fruitful field for study. Work was undertaken with Dr. Long at the University of Chicago on this basis. In order that he have certain compounds prepared he associated with himself Professor Treat B. Johnson, of Yale, and these two studies have gone on during the past three years.

I think it would be quite in line to revert again to the physical structure of the tubercle as it appears in the body. There are really four rather definite physical structures that take part in this: (1) the tubercle bacillus itself; (2) the cell called the epithelioid cell, about whose origin there is so much difference of opinion at the present time, which has its origin undoubtedly in the primary group from the mesothelium, in the embryo body, but in later life its origin is still obscure, its many names signifying this obscurity, *clasmatocyte, histiocyte, resting wandering cell*, etc.; (3) the fibrils which form the reticulum framework of the tubercle are of quite significant importance; whether they come from the fibrin of the blood, or whether they come as products of cell life in the neighborhood, is a problem also as yet unsolved; whether they act as a colloid protective agent to the tubercle bacillus or whether they act as a partial protection to the body from the outpouring of substances produced by the tubercle bacillus is also unsettled; and (4) the late appearing lymphocyte which gathers about the periphery. I only mention these four elements of the tubercle as opening avenues of attack.

I will now ask Dr. Long, who started the primary work under the Association, to present his paper under the headings which have been sent to the conference members.

DR. LONG: The biologist is impressed by the interplay of two forces in tuberculous infection,—the action of the bacillus on the host and the effect of the host on the bacillus. The direction in which the disease will progress depends on the one hand upon the virulence of the microorganism for the host, and on the other on that factor loosely termed the resistance of the host. And in the vast amount of literature to which Dr. White and Dr. Lewis have both referred, I am sure the larger bulk

deals essentially with the nature of the second of these factors. It seems to me a problem fully as fundamental as the effect of the bacillus upon the tissues of the host. And to solve this problem we must know more than we do at present of the life processes of the microörganism. In order to get at this I have tried to study its growth under the simplest possible conditions, seeking conditions even simpler than the usual ones of bacteriology and ordinary culture media.

This work began with the study of the metabolism of the tubercle bacillus in two respects; first, the substances needed for growth, and second, the substances produced during growth. I do not feel that I have made any distinct advance on the first phase. All this was pretty well worked out thirty years ago. I have simply been able to confirm previous results on the simplicity of growth requirements. There are only three or four substances absolutely necessary for growth of the bacillus, namely, an amino group or ammonium salt, glycerol, phosphoric acid, and a very few inorganic salts. Nor is the bacillus very particular concerning the reaction at which it will grow, thriving as it does between limits which modern chemistry designates as pH 6.4 and 7.8. The most striking fact to me in this review of the nutritional requirements of the tubercle bacillus is its extraordinary glycerophilism. The bacillus likes, or practically must have, glycerol. And I think we must take this feature into account if we are to understand its differences from other microörganisms.

Another striking feature in the chemistry of the tubercle bacillus, known for forty years, is its high wax content. This bacillus thus differs from other microörganisms in two respects, its high wax content and its marked glycerophilism. I have attempted to correlate the two features, and to a certain extent have succeeded, by means of a comparison of the glycerol requirements and wax content of other acid-fast bacilli, in the following manner. There is, as you know, a large group of acid-fast bacilli—some fifty have been described—but one can finally reduce them all to a few groups. On a nutritional basis I have designated three. There is the tubercle-bacillus group, including the human, bovine and avian types. Next, there is a group of microörganisms leading a semi-saprophytic existence in fish, frogs, turtles and other cold-blooded animals, and to this nutritional group may be added a puzzling misfit, the leprosy bacillus. Finally there is a larger group, including bacilli found in smegma, grass, the bovine alimentary tract and excretions, milk and elsewhere, fairly widely distributed in nature.

Now it is a striking fact that these three groups differ chemically and nutritionally on just the two points to which I have called attention. The higher they are in wax content the more necessary it appears for them to have glycerol in the culture medium. Although this is not proof, it is at least suggestive that glycerol is a wax progenitor. Another suggestive feature is that the microörganisms least glycerophilic and low in wax content are at the same time least pathogenic. There are sufficient exceptions, however, to warn us not to draw too broad conclusions on this basis.

No discussion of the chemistry of the tubercle bacillus and the other organisms of its group should fail to take account of their distinguishing characteristic of acid-fastness. Two explanations are current concerning acid-fastness. The commoner one, and the one copied from textbook to textbook, is that the staining property is due to the presence of an acid-fast wax in the bacillus. Ehrlich, on the other hand, the original discoverer of the property, attributed it to a relative impermeability of the envelope or protoplasmic substrate. My results conform with the second rather than the first of these hypotheses. It has long been known that mere mechanical disintegration of the bacillus, which certainly removes no wax, destroys acid-fastness. This disintegration can be carried out in chemical as well as mechanical ways. It is known that prolonged defatting of the bacillus does not remove its acid-fastness. If, however, the defatted but still acid-fast organisms are treated twenty-four hours with some hydrolytic agent, as weak hydrochloric acid, acid-fastness is completely destroyed. At the same time, a certain amount of "fat" previously not extractable is freed from its protoplasmic combination so that it is easily extracted with fat solvents. Briefly, on the basis of these findings and others, I have come to the conclusions that acid-fastness is due to a protein-lipoid combination, not readily permeable, but rather readily hydrolyzed, and also destroyed by vigorous mechanical means, as prolonged grinding.

So much for the substances needed for growth. Now as to the products excreted. First, as every one knows, there are certain changes which take place in the culture media in which tubercle bacilli are growing. This fact was brought out years ago in Theobald Smith's work, and used in the differentiation of microörganisms. The culture medium may become either acid or alkaline. Acids and alkalies are produced; or, possibly, one or the other is withdrawn, leaving a preponderance of the other in the medium.

In studying this phase of the metabolism of the bacillus I considered first the amino acids. Amino acids are neutral substances, containing, however, both basic and acid elements, which in a sense neutralize each other. It is perfectly possible that the bacillus could use one of these elements more rapidly than the other, and in this way changes in reaction could be produced. Another factor we cannot afford to neglect is the possible variation in another buffer, the phosphate present. The bacillus takes in a good deal of phosphoric acid, first and last, from a neutral mixture of phosphate salts, leaving the alkaline base behind. In addition to these factors operating to modify the reaction of the medium, there is the scarcely questionable addition of acid products from the metabolism of glycerol. We have applied in this study more modern methods than were available to Smith, and have found such great inconstancy in the results as respects differentiation of human and bovine strains that we have not followed this phase of the phenomenon but have rested content with the fact that both acid and alkali may result in the ways indicated.

A considerable portion of the funds which have been extended to me by this Association has been devoted to one problem, which so far has not met with success, namely, the attempt to isolate the acid decomposition products of amino acids. We have used in this study the amino acids, alanin and imidazol-alanin, or histidin. So far we have only established that the corresponding amines of these amino acids are not produced. We have failed, however, to find lactic or pyruvic acids, which might be expected in the alanin medium, and are at present engaged in the search for the corresponding imidazol compounds in the histidin medium.

So much for the acid and alkaline products of excretion. The product of excretion which has the most immediate practical interest is tuberculin, and at the present time my efforts are concentrated on a study of the nature of this substance. In the course of this work a new type of tuberculin test has been devised. With all due deference to the excellent work and remarkable results obtained by the tuberculin skin test in the past, I think it still leaves room for improvement. A fact that is becoming more and more appreciated is that the skin is by no means the only tissue of the sensitized animal which reacts to tuberculin. Probably all tissues are capable of responding. Now it is a law in pathology that the higher the degree of specialization in a cell the more susceptible it is to injury by deleterious agents. Of all the cells in the

body, none, if we except the central nervous system, are more highly specialized than the germ cells. Hence the germ cells of the sensitized animal might furnish an exceptionally sensitive indicator in the tuberculin reaction. As a matter of fact, they do. Tuberculin, which is practically nontoxic for the testicle of a normal guinea pig, is frightfully toxic for the testicle of a tuberculous guinea pig. Profound degeneration, going on to necrosis, follows its introduction in small amount. Furthermore, the injury is permanent. A skin reaction is ephemeral, but the injured testicle never returns to normal. At the end of a month there is an extraordinary picture in which atrophied germinal tubules are surrounded by actively proliferating interstitial cells of Leydig. As I carry the test out, I inject the left testicle of two tuberculous animals. The right is left uninjured for control. The animals are killed, one after two days and the other after four weeks, and the early and late response studied microscopically. Normal animals are similarly treated for comparison. All this is very complex as compared with the skin test, but I feel that there has been a corresponding increase in the delicacy of the test for the active principle of tuberculin.

At the present time I am working on tuberculin prepared from very simple media, the essential constituents of which are an amino acid, glycerol and phosphoric acid. As Dr. Zinsser has emphasized in his extensive work on tuberculin, it is still undetermined whether the active principle of this extremely reactive substance is a protein or not. All the ordinary preparations of tuberculin from glycerol-broth give protein tests, but of course protein was present in such culture media in the beginning. In the course of growth of tubercle bacilli on simple media such as I have referred to, protein sometimes appears in the medium in chemically detectable amount. Such media are active tuberculins, but this does not necessarily mean that the protein which has appeared is actually the active principle of tuberculin. It may be merely an incidental product of autolysis. On the other hand, the failure to find protein by chemical tests in a number of similarly prepared media which are active tuberculin preparations does not exclude the possibility that protein is present. Wells has shown that a protein such as coagulated egg white may be dissolved in distilled water in such minute amount as to be absolutely undetectable by chemical means and yet be readily identified by the delicate biological tests.

I would like to take advantage of this opportunity so ask the chemists present what are the most delicate chemical tests for protein. And also

will they discuss the limitations of the biuret test? The most delicate tests for protein are not chemical, to be sure, but I feel that we should exhaust that field before devoting our attention entirely to the mechanically more difficult biological tests.

I have been occupied of late with the old question of the antigenic nature of tuberculin in normal animals, using, however, a tuberculin prepared from very simple media. Repeated injections of this substance in increasing quantities into normal rabbits have led to no production of precipitins for the tuberculin used. Nor does the serum obtained have the slightest inhibitory effect on the action of tuberculin on a tuberculous animal. This failure of antigenic action rather speaks against the protein nature of the active principle of tuberculin.

Other experiments have had to do with the solubility and stability of tuberculin. It is of course one of the oldest observations on tuberculin that the active principle is precipitated in alcohol. I was interested in seeing whether precipitation occurred equally well in acid and alkaline solution. As far as I could see, on adding twenty volumes of alcohol to tuberculin made acid with acetic acid and tuberculin made alkaline with ammonia, precipitation was complete in each case. Nothing capable of eliciting a tuberculin reaction remained in solution in the alcohol.

The stability of tuberculin I have studied with respect to oxidation and reduction and prolonged standing in alkaline and acid solution. Oxidation and reduction were carried out by suspending freshly precipitated palladium black in the tuberculin and passing in oxygen and hydrogen respectively. The former appeared to weaken the tuberculin in the course of an hour, although not to destroy it, while the latter had no destructive action at all. Prolonged standing in tenth-normal alkali also seemed to weaken tuberculin, while acid of the same strength had no effect.

A few experiments of less definitely chemical nature have also been carried out. It seemed of interest to determine if tuberculin, so toxic to sensitized tissue but nontoxic for normal tissue, could be made toxic for normal tissue by treating it for a while with the macerated tissue of a sensitized animal. Tuberculin was treated for some hours with the crushed skin of a tuberculous animal and then injected into the testicle of a normal guinea pig. I have not been able to examine the sections yet, but I feel that the testicle reaction should be a delicate means for settling this old problem.

Other experiments on the nature of the tuberculin reaction in relation to infection I have been carrying out in association with Dr. Miller of Wisconsin. We have been working on the proliferative side of the reaction, a phase which Dr. Krause has repeatedly called attention in recent years. Dr. Miller has recorded the abundant development of reticulin in the tubercle, and the variation in the amount in different forms of the disease. Together we have studied the development of reticulin in sensitized and nonsensitized rabbits and guinea pigs. So far we have reason to believe that, associated with the more rapid proliferation in the tubercle in the sensitized animal, there is a speeedier and greater production of reticulin.

Finally, as to proposed lines of attack, I intend to keep on with the study of the problems I have just outlined. The general direction of the work will be toward the preparation of a purified tuberculin and an understanding of the chemical nature of the active principle. I believe that in the testicle test I have a very sensitive indicator for the presence of this active principle. Then I expect to continue coöperating with Dr. White and Dr. Miller on the deposition of reticulin and allied substances in the tuberculosis of sensitized and nonsensitized laboratory animals.

As to the bearing of these lines of work on the general problem, I think I do not need to say a great deal. Obviously they are not directed toward an immediate cure of the disease. They are so directed, however, indirectly, in the same way as any other line of research directed toward an understanding of the nature of the disease. And for a full understanding of the nature of the disease we must have an understanding of the nature of the tuberculin reaction, which enters so prominently into the symptomatology of the disease. And that calls for more definite information of the nature of tuberculin itself. I believe this completes the topics listed in Dr. White's outline, and I am very anxious to hear these questions discussed.

DR. WHITE: I will ask Professor Johnson to outline his work before lunch and take up the discussion with the consultants after lunch so that you will have the whole material up to date in front of you.

DR. JOHNSON: It is very pleasant for me to be here this morning and have the opportunity to get the viewpoints of men in related lines of activity and I am not going to introduce any revolutionary features, but I am going to confine myself strictly to the chemical viewpoint of this important question. In the first place, I should like to give due

credit to Dr. Long for interesting me in this subject. It is due entirely to him that I was called into this work about two or three years ago. I suppose he thought I was the proper individual to approach because I had done so much work on pyrimidine chemistry. Funds were provided whereby I was able to induce Dr. Brown, one of my graduate students, to take over this work. He spent two years on it, and as a result of his work he was granted a Doctor's degree at Yale University. When we got pretty well started on our problem I concluded that we had located a man who could produce and do us some good by working in this field. Fleischman and Company of New York City thought he would be more valuable in their plant than on the Yale campus and consequently doubled his salary and took him away from us. Since then, due to illness and lack of another coöperator, the work has been at a standstill.

In the second place, I should like to name the sources of material used. Dr. Long provided me with a small amount of tubercle bacilli which had been defatted. The Parke, Davis Company and Mulford and Company placed at my disposal about 800 to 1,000 gm. of dried tubercle bacilli which were in a very bad state when I received it. It was badly contaminated, and quite a lot of work was required before I actually succeeded in obtaining a product which would permit careful chemical investigation. Allowing for losses in material, I succeeded in getting 436 gm. of pure defatted bacilli after extracting 43 per cent of fatty material. I worked with all kinds of solvents for getting good defatting results, and finally decided to use toluene, and that is what we came to use in all our work. From that 436 gm. of fat-free and dried tubercle bacilli 7.7 gm. of tuberculinic acid was isolated. The product failed to respond to the biuret test for proteins and gave all the reactions and tests which are characteristic of nucleic acids. I was dependent upon protein reactions which were used by co-workers in my university, namely, Osborne, Mendel and others, and in fact the material was thoroughly tested by Dr. Brown; so I assume that my material was protein-free so far as it was possible to judge by chemical test. The nucleic acid was subjected to acid hydrolysis and an analysis made for the pyrimidine content. We have had a good deal of experience in our laboratory in handling these combinations. We have been working on delicate color reactions and have developed new reactions whereby we can detect thymine, cytosine and uracil in very dilute solution, and the use of these tests helped us to solve the problem that we were asked

to solve. Our conclusions already published were as follows: in the hydrolysis of nucleic acid (tuberculinic acid, the nucleic acid of tubercle bacilli) we applied acid hydrolysis by digestion with sulphuric acid and then made an analysis for pyrimidines. Cytosine and thymine were separated and identified. Uracil was not found in the molecule of tuberculinic acid.

We were absolutely unable from any point of attack to show the presence of uracil. I will go back to that question later because I think there is a great deal of confusion here and I think a great many errors have been made in drawing conclusions from the test for uracil. From this 7.5 gm. of nucleic acid we succeeded in isolating pure thymine and cytosine, and these were analyzed and proved to be such from the charateristic tests. The residue that we had left after we had removed the nucleic acid was absolutely free, so far as we could judge, from any pyrimidine and purine compounds. It was highly contaminated with inorganic material containing phosphorus but failed to give any test which would lead us to believe that it contained nucleic acid. We repeated all the work on 810 gm. of tubercle bacilli furnished by Parke, Davis and Company. That yielded, again after complete analysis, the same pyrimidines, and we isolated both thymine and cytosine but could detect no uracil. In this hydrolysis we paid very careful attention to the question of sugar. We ran through a lot of tests for carbohydrates. The hexose sugar predominated and while we could get some evidence of pentose it was in very small amount. Through the formation of levulinic and formic acid by hydrolysis we concluded that a hexose sugar is the carbohydrate functioning in this nucleic acid.

Having isolated and identified the pyrimidines, which was the problem of major importance as submitted to us, the next problem to receive attention was that of obtaining some idea of the constitution of the acid. Here we started with 596 gm. of tubercle bacilli, which the Mulford laboratory furnished, and we isolated 15.8 gm. of nucleic acid. This is a yield of 1.75 per cent of nucleic acid based on the quantity of tubercle bacilli started with.

We made an observation here which is of particular interest to me, and which I hope to follow up if we keep up with this work. Intense hydrolysis did not lead to a distinction of cytosine with production of any uracil. It is a well-known fact that the amino purines undergo such a transformation under the influence of hydrolytic agents and enzymes. Tuberculinic acid was proved to be very susceptible to hydrolysis and is

apparently a trinucleotide, and we obtained guanine entirely split off from the original nucleic acid.

Now having shown that we are dealing here with pyrimidines, the question comes up from the chemical point of view, can uracil come from cytosine? We have knowledge, for example, that the purines, guanine and adenine, are autolyzed or hydrolyzed in animals over to xanthine and hypoxanthine. In other words an amido group can be removed from these combinations. We have had a great many observations made reporting where uracil has been shown to be present, and many have drawn the conclusion from such results that the nucleic acid that produced this complex did not contain it but that it resulted from its precursor, cytosine. This question is a very important one. Has any enzyme been found which will convert cytosine into uracil in the same sense that guanine will go over into xanthine? It is an important point if so; if such an enzyme can operate and this molecular change can be brought about in that way, we are surely drawing the wrong interpretation with respect to the structure of nucleic acid in the cell. Fortunately, I ran across a paper the other day published by a Japanese investigator in which he states that he observed that cytosine, when subjected to the action of pancreatic enzymes, is converted into uracil. If true that is an important result from the chemical point of view.

Now another point that I want to bring out, absolutely fundamental, is that I am quite certain from what I have observed that the removal of the amino group from cytosine to produce uracil is a more difficult proposition than when cytosine is linked in a nucleic acid. It influences, for example, the ease with which the amino group can be removed. That is a purely chemical question and has an important bearing on this question of structure. The conclusion that we draw up to date is that tuberculinic acid, isolated from tubercle bacilli under best methods, does not contain uracil in the molecule of tuberculinic acid, but is constituted of two pyrimidines, cytosine and thymine, and two purines, guanine and adenine. There are a great many ways in which these four units can be linked together. I think that we have very definitely established the fact that uracil does not function in the tubercle bacillus.

Now in regard to the material on hand. I have in my laboratory to-day 1115 gm. of tubercle bacilli which contain 1.5 per cent of water, which has been provided me by Mulford's Laboratory and Parke, Davis and Company. In addition to that I have all the protein which has resulted from my hydrolysis experiments, which comes from all of these

operations that I have carried through. In fact, I have half a kilo of the protein which has been freed from nucleic acid so far as we are able to do so. I have also in my laboratory, preserved in toluene to prevent putrefaction, for future investigation, a very large quantity of extractable material. Every gram of this material has been saved. I have made every effort to preserve material in its original condition, if toluene and chloroform are sufficiently strong antiseptics to prevent enzymatic changes. It is important to get the consensus of opinion of this Committee in order to work along lines whereby we can direct further attention profitably to the investigation of this material.

Let us go now to the next point, the proposed plan of attack. Personally, I am intensely interested in determining and ascertaining in some way a chemical classification for bacteria. Can we do it through an analysis of the nucleic acid of the various cells? It seems to me that we must get down to some fundamental basis. That to my mind must be chemical. Can we base a classification on results from analysis of nucleic acids? I find by looking over the tuberculosis literature that the situation in regard to the proteins is simply chaotic. We have practically no definite evidence regarding the true character of the proteins in tubercle bacilli. Read the literature of fifty years ago and you will have to throw away 80 per cent; it is no good to us. The methods they applied were not modern and the conclusions which have been drawn must be tested.

In regard to the tests for protein I would call your attention to certain color reactions which can be followed chemically and it is of the greatest importance in our work. We must admit that in the bacterial cell we have almost every possibility of acid-amide linkings capable of undergoing deep-seated changes. If you take glycocoll and submit it to the action of alloxan, an oxidative product of uric acid, it is converted to aldehyde. Alloxan is an oxidative product of the purine-uric acid which is capable of stimulating important molecular changes, and it is perfectly possible that such combinations may function in many metabolic processes. If we thus perform in the test-tube or in the beaker, what are we going to expect in a highly complicated substance like the tubercle cell, where every one of these changes can take place and over which we have no control? A hundred and one reactions can take place in that medium before we get to the end results.

Now, personally, I believe that the amino-acid content of these proteins can be more accurately determined. Has any one ever shown that

sulphur functions in the protein of the tubercle bacillus? From my reading I have seen no evidence that cystine actually does function as a constituent of the protein in this microörganism. Why I take particular interest in this element is because I have been working on the proteins of silk. Silk is generated under specific conditions biologically, with which you are more familiar than I am. This protein contains no sulphur. In the light of the work of Hopkins on glucothionone it is a very important point to determine whether sulphur is needed or actually does function in this cell. From the chemical point of view this needs, I think, some consideration. I should like to see applied in the work on tuberculosis some of the modern methods of analysis to obtain a clearer picture of what these proteins are. I should like to know what types of proteins are present. Is all the sugar wrapped up in the nucleic acid, or is it linked also in some other form?

I think also that there is a dispute in regard to the question of free fatty acids of tubercle bacilli. This is a question that interests me very much. I have one man who has been working for the past year trying to develop new methods of analyzing for fatty acids. I believe I shall be able to reveal the presence of free fatty acids in dilute solution and determine them quantitatively. We have hitherto been unable to do this because of lack of refinement in our methods. The question of phosphatides is a very important one and we know practically nothing about them. Furthermore, I should like to know, for example, whether the tubercle-bacillus cell can build up in its own organism its own pyrimidines from artificial foods, or does it absorb such products from the tissues of the host? We have not yet proved satisfactorily to my way of thinking that the tubercle-bacillus cell actually does construct its own thymine and cytosine. There may be products of disintegration which have been supplied in growth. When we come to make a chemical picture of these pyrimidines I should like to find out, for example, where the methyl group in thymine originates? Where does it come from? I can take my thymine in my test-tube with a mere trace of iodine, without any acid or alkali and at zero degree break it down into simpler organic compounds. Now then, if thymine is so sensitive to these changes and can be reverted back into complexes like pyruvic acid and acetol, is it not conceivable that pyruvic acid may function in its synthesis in the cell? The question comes up, what is the function of such bodies from the metabolic point of view in the building up of the thymine? We have evidence also that nucleic acid exists in a free state in the tu-

bercle-bacillus cell. I have satisfied myself that you can take the dried bacilli and simply extract nucleic acid from that cell by treatment with water.

Now in regard to the question of tuberculin. I would like to submit whether anybody has tried to demonstrate what its specific action is due to? If tuberculin is a nucleoprotein is it the protein or nucleic acid that functions in this inquiry? It is stated that tuberculin (active) does not contain proteins. Now is it certain that these solutions are free from nucleic acid? I am not satisfied that the biologist has demonstrated that protein is the active compound of tuberculin and that its activity is not due to some constituent of a different nature. I submit as a suggestion that nucleic acid may be the active principle. I think Dr. Zinsser has some evidence that he might bring up in the discussion which might give us a little clearer interpretation.

Now the last point that interested me in all this work was the handicap we were working under on account of the lack of refined methods of analysis. I am absolutely certain that the chemist has got to reorganize and remodel his final attack if he is going to create any knowledge which will help settle this question. I am extremely anxious to incorporate in my laboratory some of the new methods of microchemical analysis. We have got to change our technique and operate under more refined analytical procedures. You cannot depend entirely upon the Kjeldahl and Carius methods of analysis for nitrogen and sulphur or the ordinary combustion methods. We have got to refine our method of attack as chemists, and one of the fields we must develop in any work we undertake in the future are methods of analysis involving technique to allow us to perform analytical operations with very small quantities of material. We are limited in our work because of our inability to analyze our products when limited to small amounts of material. I am extremely anxious that, instead of being obliged to wait to work up 1 kilo of material, I may be able to work with 100 grams and get my analytical results. In order to get these analytical results, a part of the problem, if the chemist is to help any, is to be permitted to have men drilled in technique and capable of handling these newer refined methods.

I am intensely interested in some new results just announced from Berlin in regard to the composition of protein. I refer to the X-ray methods of analysis. I have always assumed that fibroin of silk, for example, is a pure protein. X-ray analysis indicates that it is not a definite chemical compound. I should like to see other proteins submitted to that

analysis. The results might lead to a decided alteration of our present view. It is these newer methods of attack that we must make. We must go into the field with a new line of attack and with the newer instruments applicable for molecular analysis. I am very certain that the chemist can help in getting at a clearer definition of what we have to deal with in the tubercle-bacillus cell. I maintain that our present ignorance of the chemistry of the cell prevents us from making advances of the greatest importance to biological science.

From the chemical standpoint there is work enough there to keep several men busy for ten years. It is a question of ability, from whatever angle you may view the problems to be solved. It is a question also of refined chemical analysis, and we have only just begun to scratch the surface.

DR. WHITE: You have heard now the work carried on in this field under the Research Committee of the National Tuberculosis Association for the past three years. There are two other fields of work that have been going on, which I think I ought to mention because there are phases of the tuberculosis problem that are not purely chemical and are of more practical value, and before the discussion opens I should like to call them to your attention. The work of Dr. William Snow Miller, of the University of Wisconsin, on the anatomy of the lung and the structure of the tubercle has been assisted by the Association for the past three years and Dr. Miller's work, anatomic and histological, has been of great help in solving the question of the anatomic distribution of tubercles in different animals of the vertebrate kingdom. Then, as a more practical question, the problem of establishing X-ray norms, or X-ray standards of what can be considered as normal in human lungs at different ages. That work has been done by Dr. Pancoast and Dr. Landis here, Dr. Baetjer and Dr. Austrian at Johns Hopkins and Dr. Dunham, Dr. Blackfan and Dr. Morris in Cincinnati. These men have worked with interest and patience in establishing, first what shall be considered the normal pulmonary picture of children from six to twelve years of age, and this year are working on the middle adult ages of from twenty to forty. That constitutes all the work that has been done up to the present time. This is the first conference which has been held on any of these subjects. I should like before lunch, then, to ask Professor Abel, who has been kind enough to give up the day, to open the discussion.

DR. ABEL: I don't really know why I am here. Dr. White asked me to come over from Baltimore and I told him that I had not worked in this field myself, except in a very elementary way about thirty years ago when Professor Klebs first came to this country and brought me extracts of tubercle bacilli to determine whether fat substances were present in them. I had about a litre of dried bacilli at that time. You have covered a very wide range of subjects in the morning's discussion. I was very much interested in following all of the points that have been raised. I want to congratulate these gentlemen who have devoted so much time to these subjects on the positive results they have obtained. After all what the scientist must get hold of is *facts*. As Huxley once said, "A little apparently insignificant fact often overthrows the most complex and greatest hypothesis."

Now the points that were brought out in respect to the state of nutrition of the body in relation to tuberculous infection interested me. I have often wondered to myself whether the endocrine organs had anything to do with building up what the older physicians called diathesis, a congenital or acquired condition predisposing the individual to take on the tubercle bacillus easily. Dr. Lewis has presented many points, it seems to me, of the greatest importance; among these is the varying response of the test animal to the dead and living tuberculosis germ. Dr. Long's work also impressed me very much indeed. The high wax-content of the bacillus and its correlation with, or its relation to, glycerol, which he has established is, I think, a very definite step forward.

As I say, I am an outsider and can really do little more than express my appreciation of this work. The question of excreted products that Dr. Long has been working at so extensively, all that too is a problem that must be worked out more definitely if one wishes to get at the metabolism of the tubercle bacillus. A thought came to me whether anything could be done with vivi-diffusion methods in the study of the metabolism of this microörganism, whether we could employ the vivi-diffusion apparatus to separate from growing cultures balanced against a sterile culture medium certain chemical products which it might be difficult to obtain by other methods. That is a mere suggestion,—I understand you wish us to throw out suggestions, although they may not have the slightest value. Then I listened with great interest as to the question of the chemical nature of tuberculin. Professor Johnson made some suggestions that struck me as very pertinent, such as whether what we call tuberculin is free from nucleic acid. I suppose some claim they have made it so.

I have never been very much impressed with the mere statement concerning the absence or presence of a biuret reaction in a given material. This reaction, as you all know, is not a very sensitive one for many proteoses and is easily interfered with by reducing substances. In my opinion, it would be well to state the concentration of material employed in making the test. The removal of traces of proteose from other substances is often exceedingly difficult; or, to put it in another way, the removal of highly active principles, where one fails to find the sought for active principle, if one has employed methods that have removed the proteoses by adsorption. The active principle in such a case will generally be found in the precipitate containing the proteoses. Proteoses have an extraordinary power to prevent crystallization of associated substances. They thus interfere in the most annoying manner with the isolation of active principles of all sorts; as, for example, endocrine principles such as secretin, insulin and pituitrin. I suspect that pure tuberculin itself will not give the biuret reaction, although I have no real reasons to give in support of this opinion. I am finding it very difficult to separate the proteoses from the highly powerful active principle of the posterior lobe of the pituitary gland, and I shall watch Dr. Long's struggles with tuberculin with interest to see how he will solve the problem of isolation.

The problem of isolating an active principle sometimes requires decades for its solution. It required a full century of toil and labor on the part of chemists to isolate the active principles of ergot, to mention only one instance among many. It is very difficult indeed to get out active principles quite free from contaminating substances, and even when we think that we are dealing with an individual one we may nevertheless be mistaken. I was very glad Professor Johnson brought up the new facts about serine. That substance was assumed to be a chemical individual, and yet by the use of modern physical methods it is seen to be composed of two substances, a crystalline principle in association with a substance of colloidal character. And so I think that, as tuberculin is of such enormous importance, both in the way of testing and possibly in a therapeutic way in the future, its isolation should be attempted. Dr White, isn't it true that you can to some extent improve the clinical condition of guinea pigs that have been infected with the bacillus of tuberculosis by means of tuberculin injections?

DR. WHITE: Absolutely you can.

DR. ABEL: Then that is a very important lead. Suppose that tuberculin can be isolated as a pure substance and that improved tuberculins can be made, then we might possibly in the future greatly improve our therapeutic procedures in human tuberculosis. Chemical work on the tuberculin problem should certainly lead to results of great value. Of course, as I have said, this work is so enormous that it is difficult to decide what to take up. A man must take up, I suppose, what appeals to him. It is well known that things which are not important to-day will turn out twenty years hence to be very important. I personally think that it is always wise to tackle a difficult thing, and certainly it is a difficult field that Professor Johnson has been discussing. I have been listening to him with very great interest, and I quite agree with his conclusion that the chemist needs more refined methods before he can hope to solve the problems that have come up for discussion to-day. I have already made that clear when I spoke of the difficulty of separating active principles from albumoses.

We have therefore in this department of chemical work the greatest uncertainty at the present time but progress is being made. I quite agree with Professor Johnson as to the need of finer analytical methods and I can say from my own experience that the Pregl methods are certainly splendid. Some years ago Dr. Hans Lieb, one of Pregl's assistants, very kindly made a number of analyses of certain crystalline substances which I had been able to obtain in the pure form in very small amounts only. For example, I sent to him at one time about 20 mgm. of a certain hydantoin (alpha-isobutyl-hydantoin) which my co-workers and I had obtained from the blood by vivi-diffusion. Dr. Lieb made two concordant carbon and hydrogen analyses of this compound, using 4 mgm. or less for each analysis, and two concordant nitrogen estimations, and returned to me more than 4 mgm. of the hydantoin which he did not need. With this small quantity of about 16 mgm. the molecular empirical formula $C_7H_{12}H_2O_2$ was obtained. By the older combustion methods we should have required close to 1 gram of this crystalline material to obtain the same results. As Pregl's microchemical methods can be applied to other elements, such as sulphur, chlorine, etc., it is not surprising that it is admitted that his methods constitute the greatest advance that has been made in analytical chemistry since Liebig's time. I merely mention in passing that I visited Pregl's laboratory at Innsbruck in 1913 and made arrangements with his assistant, Hans Lieb, to come to my laboratory to teach the new methods to my staff

and the staff of the department of organic chemistry. A microbalance and the other necessary apparatus was purchased, but the outbreak of the War prevented the carrying out of my plans.

The structure of the nucleic acids present in the tubercle bacillus should also be worked out if possible. To return once more to a remark I made at the outset, we are dealing with a subject of very great extent, and in this broad field one may have to make a choice of subjects for study. Carl Ludwig used to say that everything depends upon the precision with which one outlines his *Fragestellung*. Success often comes very quickly to one if one has formulated wisely and clearly the question that is to be attacked. I have been very glad indeed to see that the members of your Committee and the gentlemen working with you have held this idea very clearly in mind. In every case the *Fragestellung* has been as clear-cut and precise as it could be made.

DR. WHITE: There is no need for any of you gentlemen to apologize for being here. Your presence was the subject of a great deal of thought and care. We want you to know that Dr. Abel was chosen because he is really the sole representative in this country of physician, pharmacologist and chemist, and his kindness in coming over we appreciate very greatly and his discussion we appreciate. Dr. Richards was chosen because of his work with Professor Dale on the endothelial cell, its permeability, its structure, and its susceptibility to poisons, and as the developer of exquisite new methods of study. These subjects are related to tuberculosis, as you see from the discussion. Dr. Zinsser was asked because he is a representative student of the question of body resistance. Dr. Levene, of the Rockefeller Institute, was to have been here, and I am sorry he is not, as you all are; but our purpose is to bring into discussion correlated fields of research and throw light, if possible, on the tuberculosis question.

Adjourned for luncheon at 12:45 P. M. to meet at 1:45 P.M.

Afternoon Session

The Chairman, Dr. White, called the meeting to order at 2 P. M.

DR. WHITE: In opening the afternoon discussion, it seems to me worth while at the beginning to say one or two words in connection with the purpose of the National Tuberculosis Association, which has for fifteen years exhibited an honest and anxious endeavor to relieve the

suffering entailed upon those who become infected with tuberculosis beyond their resistance point. Those who have discussed the question here and who will be asked to discuss it are naturally doing so in that spirit, in an endeavor to relieve human suffering. The frankness with which those who have been associated with us in research have expressed themselves this morning must be apparent to you all. In the carrying on of your discussion I want to impress upon you that every man in this room will guard with the utmost confidence the things which you say, feeling that they are yours to give as you wish and they are ours to use only for one single purpose which is that of the Association;—the relief of suffering. I am going to ask, this afternoon, Dr. Richards to open the discussion; Dr. Zinsser to follow; Dr. Opie to follow Dr. Zinsser; then members of the Committee to follow; Dr. Opie, Dr. Long and Dr. Johnson to close the discussion; and then we will attempt to put down an approval of the things upon which we are all agreed. We will leave out those things about which there is not agreement for the present. It is my own hope and that of the rest of the Committee that in this correlated work the substances produced by, for instance, analytical work on the tubercle bacillus, shall be available to anybody whom, we will say, the Committee approves to carry on their work. Dr. Richards, will you continue the discussion?

DR. RICHARDS: I think there is no one sitting at this table who is less possessed of knowledge of this subject than I am. I take it that the only thing I can contribute is the thoughts,—many of them, all of them very vague,—which occur to one who is engaged primarily in physiological research. I have no intimate acquaintance with the definite problems of tuberculosis. I have had an opportunity of friendship with Dr. Lewis and of frequent talks with him, so that a little reflection of something of the problems of tuberculosis has come to me in that way and only in that way.

In so far as I am expected to discuss the papers of Dr. Long and Professor Johnson I can only say that it is extraordinarily difficult for me to visualize the results and the projects which they have outlined so well, to visualize the connection of these results with the more immediate purposes which such a Committee as yours must have in mind. They are tremendously important in the chemistry of the tubercle bacillus, beyond any question. The relationship between chemistry of the substances extractable from the dead bacilli and the conditions of growth and spread within the body is something that is almost beyond—it is beyond

my imagination. Dr. Long's paper seemed to me to be extraordinarily helpful and beautifully presented. He is a past expert on the questions he asked as to progress, and I cannot think of any question he brought up which he has not advanced and which he is not in a position to advance still further as he goes on. It seemed to me extraordinarily stimulating. Whether I am expected to say something on more general aspects or not I do not know.

DR. WHITE: Yes, Dr. Richards.

DR. RICHARDS: But I have these thoughts, if you call them thoughts; they are very vague. I am wondering what I would do if suddenly placed in the position of being obliged to work for this Committee, or some organization, upon the subject of tuberculosis. Where would I try to strike in? My experience has been in connection with problems of pharmacology. In the teaching of pharmacology some of the easiest things we have to teach, the action of drugs on the circulation, let us say, a good many of them are quite valueless, I am sure, from the standpoint of the estimation of what a drug may do in assisting a body to overcome a disease process. It seems to me that there is a vast field in the analysis of the normal body, acting in an optimal way, and reacting to physiological or detrimental circumstances; and if I could gather around this table such men as Barcroft, Starling and Dale, people who have spent a lifetime in the study of the circulation, I might devise a system of experiments which would interpret for me the variation in which the normal body reacts to untoward conditions from the standpoint of the circulation. I might from such conference outline a program in which I could analyze the variation in which the normal circulation, or rather a slight deviation from the normal, is concerned in the problem of resistance to tuberculosis, in the problem of the spread of tuberculous infection, and so on.

Such men as Barcroft and Starling would discuss a matter from the standpoint of gross changes, changes in the organ, gross changes in the body at large. If we could enlist in such discussion the advice of Krogh, he might turn our attention to the immunity changes within a single organ. It seems one of the finest things in physiology in a long time to show that the circulatory apparatus in a single organ does not necessarily act as a unit, that at times a portion of it is affected, and at other times all of it is affected; and I have had the fortune in the last two months to find in the case of one organ that a very slight deviation from the normal may result in the production of a condition which you would

call pathological, but quite specific. It has been known for a long time that the mechanical interruption of the circulation through the kidney leads to albuminuria; we find it true that if you compress the renal artery for a moment albumin occurs in the urine, which shortly afterward clears up. You can duplicate that experiment by injecting a little adrenalin into the circulation. You can interrupt the circulation through enough of the kidney to produce a transient albuminuria. It is easy to imagine that such a change is on the verge between normal and pathological, and that one organism might be slightly more susceptible to such a change than another organism.

I am trying to visualize for myself certain changes connected with the circulation which might be concerned with the variation in which a circulation would react to detrimental influence such as actual bacilli or the products of bacilli. The question of capillary physiology is one which throws light on the question of gross physiology of organs; and it seems to me that if physiologists are to be enlisted in such a field of investigation as that represented by tuberculosis that type of investigation should be represented. I have been wondering, too, what would happen if, let us say, Professor Ross Harrison were brought to this board and, let us say, collaboration between Ross Harrison, Meyerhof and Warburg. Meyerhof has shown some beautiful things connected with the metabolism of very minute aggregations of cells,—connected with the physiological-chemical properties of these. Could anything be gained by a plan which such men might formulate in connection with the symbiotic growths of tubercle bacilli with living cells under simple conditions of the sort Dr. Long is interested in, in his attempts to make tuberculin? I cannot contribute to your program, Dr. White, you see.

DR. WHITE: You are, Dr. Richards.

DR. RICHARDS: I don't think I shall try any more. It seems to me that these minute questions of capillary physiology, the reaction of the whole body to physiological influences and to abnormal influences brought into existence in such an affection as this, are of first-rate importance. Permeability of capillaries is something which has been talked about in the last few years quite intensively and about which we know very little. Light is coming, or rather questions are arising as to whether in what we think are ordinary physiological processes we are right about this or not. The question of filtration through endothelial membranes may be a process which is quite different from that which we

thought it to be. The Donnan equilibrium is something which is in everybody's mouth, and what the Donnan equilibrium may mean to physiology we are still quite in the dark about. If it were in my power to suggest I would suggest that such work as Krogh and his followers have done on capillary physiology, that such work as Meyerhof's and Warburg's on metabolism and respiration, with work of that sort, be examined for the leads that might come out of it in connection with such work as yours.

DR. LEWIS TO DR. RICHARDS: This may be a little unfair, but from the point of view of these suggestions that there may be something in this field, would you feel that we were to-day advanced to such a position that we should consider it within the realm of possible experimentation? Must we consider that these things are mechanical in the sense that we are dealing with membranes that act as though they were dead, or must we still take into account at every step that we are dealing with living cells?

DR. RICHARDS: We must take into account that we are dealing with living cells. I think of the properties of dead membranes in so far as they are arranged in very minute tubes, and contain on one side a fluid of one composition and on the other another. There are many questions to be still explored. It is possible by means of a dead membrane to separate one salt from another, both of which are diffusible from that membrane, but have different rates of diffusion. It is possible to increase the concentration of the electrolytes on one side of a membrane in contrast to another in accordance with the Donnan equilibrium, as I visualize it. My point is this: that the behavior of dead membranes is not known and, to a much less extent, the behavior of living membranes.

DR. LEWIS TO DR. RICHARDS: We have, of course, to approach the matter as persons who are extremely far away from their field and, supposing you had decided to make a start in such a direction, it might be a choice as to whether to start from the dead membrane, or directly with the living animal. I take it that from your point of view both ways have to be kept in mind and that the choice would be rather on the basis of the particular interest of the individual worker and his particular capability to handle the subject in a particular way, rather than on that of any preconceived idea of what was best.

DR. RICHARDS: If I can answer that suggestion, or question, on the basis of a very personal experience it would be in this fashion.

Work was done in my laboratory last year which showed me, as I think beyond a doubt, that a blood containing 0.4 per cent of sodium chloride in its plasma could yield a glomerular filtrate containing 0.5 per cent sodium chloride. I propose to investigate that phenomenon further by just perfusing through frog's kidneys fluid plus formaldehyde plus alcohol, and see whether I can do so. I am inclined to think I can. We have no distinctions between the dead and the living membranes.

DR. LEWIS TO DR. RICHARDS: I think you have helped me very much.

DR. WHITE: The cell that lines the capillary and its relation to the physical structure of the tubercle is certainly an open door for study. And while you would in your modest attitude, Dr. Richards, feel that you have contributed nothing, I feel personally—and I am sure that the others feel—that you have contributed enormously.

DR. WHITE: Dr. Zinsser, will you continue the discussion.

DR. ZINSSER: I shall not waste your time by thanking you for the opportunity of hearing Dr. Long's paper,—a thing which I say not in the way of the usual casual congratulation. His work has impressed me as particularly notable for its common sense and the simplicity of his approach to this difficult problem; it has made considerable progress in the right directions, in my opinion. Our own work was started from a different point of view, namely, that of the bacteriologist interested in the relationships of allergy and immunity. The best manner in which I can help you in this survey of investigation of tuberculosis is to imitate the splendid frankness with which Dr. Long reported his work. I will, therefore, discuss our work in the light of not only the finished but also the unfinished experiments, and will incorporate not only my own views but those resulting from the studies of some of the assistants with whom I have had the good fortune to be working. Dr. Abel has emphasized the great difficulty of the problem.

The first question, that of the nature of tuberculin, is perhaps the most important distinct problem. My interest in the tubercle bacillus in this connection was largely due to the fact that with this microörganism it was easiest to approach certain general principles of bacterial hypersensitiveness, mainly for the reason that one could easily obtain large quantities of the bacilli for chemical manipulation, and one could produce chronic disease in laboratory animals. The principles that were elucidated with tuberculins have since been applied by us to other microorganisms.

One thing has been unfortunate in the chemical analysis of bacterial substances, namely, that most of it has consisted in elementary analysis of the bacteria grown in large amounts, with total nitrogen, hydrogen, carbon, etc., determined without consideration of the functional relationships of the different chemical compounds in the bacteria to the manifestations of infection. The importance of Dr. Long's method of approach is apparent to us. In this we worked with the same idea of attempting to find out something about the chemical definition of the compounds that were of actual biological significance in as unchanged a chemical condition as possible. It did not seem to us to be very interesting to study the chemical fractions of the bacterial components after, by cleavage or other manipulation, they had lost their biological properties. A great deal of whatever success we may have had in casting light on the chemistry of these substances is to the credit of my associate, Dr. Mueller, who assisted me with the chemical approach and has since then carried out independent studies of his own.

Unlike Dr. Long, we obtained our tuberculin from the bacilli themselves, drying them, grinding them and extracting them with weak alkali. The further treatment of these extracts is familiar to Dr. Long and the rest of you; but, to recapitulate, they are precipitated with acid, causing in this way a very heavy precipitate which we speak of as *phospho-protein* and *nucleo-protein*, although probably this fraction contains a considerable number of other things. After filtering off this, we boil the residue at a pH of 5 and remove the coagulable proteins as far as we can. As a matter of fact, very little comes down. If filtered while hot and permitted to cool, we then sometimes were able to obtain and remove a moderate amount of Bence-Jones protein. After this we have a water-clear fluid, from which an alcohol precipitate can be obtained which is active as tuberculin. This substance gives excellent skin reactions, essentially identical to those obtained by O. T., etc. This we call the *residue material;* and entirely analogous materials by similar methods have been obtained since then from all the other microorganisms which we have investigated: influenza bacilli, pneumococci, staphylococci, meningococci and, recently, gonococci. These substances give skin reactions and precipitates specific with homologous sera; in fact the specificity is so great that the pneumococci types can be thus identified. These substances give no Biuret reaction, no sulphosalycilic acid reaction, no Hopkins-Cole, and none of the ordinary qualitative protein reactions except a very feeble xanthoproteic reaction.

To this we have attached some theoretical conceptions concerning the possible presence of an aromatic amino-acid group in the substances, a point which, however, is too theoretical to enter into here. Dr. Mueller is actively analyzing these materials, and is now beginning to obtain results on the structure of tuberculin, which eventually may corroborate the work Dr. Long is undertaking.

Since these substances do not produce antibodies when injected into the animal, but react with antibodies in the test-tube, we may say we have a substance corresponding to what Ehrlich might have called the *haptophore group;* and we believe these substances, in general, correspond to the materials Dochez and Avery found in the urine of pneumonia patients. The only possible method of finally proving that these substances are entirely nonprotein will be by analysis. Last year, with the help of Mueller and Weyman, we attempted this on the bacteria, but, since the material obtained was scant, we drew no conclusions from the experiments. Mueller is now attacking the problem with residues obtained by him from yeast, and with the tuberculin, and is making more encouraging progress by methods developed by him. He has found an experimentally low nitrogen content, and believes the material is very largely carbohydrate. The material is nondiffusible and, when made from tubercle bacilli, will withstand three atmospheres in acid reaction without destruction. The chemical solution will come when we obtain a sufficient amount of the material for accurate analysis. That it is not nucleic acid is apparent from its nondiffusibility, so far, and from the small percentage amount of nitrogen found in the acid material. Also, it is much more resistant than nucleo-acid to chemical manipulation.

We are now interested in trying to find out what the source of this material is in the bacteria, and we suspect that it is a cleavage product of the nucleoprotein. This opinion is based on the fact, experimentally demonstrated, that living bacilli during growth produce this material with a speed and in a quantity far superior to that with which it can be extracted from dead microörganisms of far greater quantity, and because the tuberculin effects obtained with it can be similarly obtained with the unbroken nucleoprotein. This is now being experimentally investigated. It is still not impossible that in the residues we are dealing with a very small amount of nucleoprotein in solution, and the difficulty of excluding this is easily understood if one considers the work on protein solubility carried out by Cohn in Dr. Henderson's laboratory. Work like that of Dr. Long and Dr. Mueller, who are chemists competent to apply

logic along the main routes of investigation, will probably arrive at a solution. The pure bacteriologist can do no more than encourage, and fundamentally check up their results by animal tests. However, it is already clear that in tuberculin we are dealing with a substance that is not unlikely to prove a protein, which is probably molecularly simpler than protein and, being represented by analogous substances in other bacteria, it is probably of great importance in the pathology of infectious diseases. The theoretical consequences of the reasoning which we have applied in several publications to these relations may be omitted in this discussion.

All the investigations with these substances in regard to skin reactions seem more and more to point out to us the importance of Dr. Richards's remarks, which, with his habitual modesty, he did not make as emphatic as he was entitled to make them,—that it is a fact that the question of capillary permeability is probably deeply involved in the processes.

Our other lines of investigation have followed the not entirely original conception that there is a relationship between tuberculin hypersusceptibility and resistance to tuberculosis and in the hope that we might understand this mechanism with the purpose of producing artificially the kind of hypersusceptibility and, therefore, protection, which spontaneously takes place in man by the early tuberculization of most individuals living in civilized surroundings. The first step in this investigation has been made, we think, by the discovery, together with Petroff, that typical skin hypersusceptibility can be produced in guinea pigs with dead tubercle bacilli. A great deal of valuable preliminary material for our work came from investigations such as those of Baldwin, Römer and Krause. In no line of investigation ever undertaken by me have I obtained so much help from previous investigations, nor been able with such ease to confirm the assertions of those who have worked before,—a gratifying experience. There are still many difficulties to overcome, and progress will necessarily in this subject be slower than in other lines of investigation. Incidentally, we are again investigating passive sensitization,—but this has not sufficiently progressed to permit of any kind of statement that would be helpful,—involving the problem of the assertion of Besredka that different parts of the body can be unequally sensitized by local methods. This is the line along which we are approaching this question, a matter which I am stating only in order not to withhold anything that is in my mind, but without the im-

plication that we have made any progress. The question of the production of toxic compounds by mixing tuberculin with tissue and serum, with the idea of producing toxic cleavage, I am not in sympathy with, simply because it does not fit in with the line of reasoning at present most attractive to me, but without any idea of discouraging efforts in this direction. I believe that the unchanged tuberculin acts upon the sensitive cells in which the state of sensitiveness depends upon an increasing accessibility of the cell body to the substances. In this, I think, lies the secret of the difference between the normal and infected sensitized animal. This leads us to the extremely difficult problem of cell permeability, to which I see no immediately promising method of experimental approach, but toward which the coöperation of the physical chemist and the bacteriologist, and work such as that of Loeb, is pointing a path.

In concluding I wish to thank you again for the opportunity of being here, although I feel that in actual participation I have merely enjoyed myself in going over my own thoughts with the possibility of receiving suggestions.

DR. WHITE: Dr. Opie, will you go on with the discussion.

DR. OPIE: I have found this symposium on the relation of chemistry to the biological problem of tuberculosis very profitable. It is evident that we shall need much assistance from chemists before we can define the biological phenomena of tuberculosis in chemical terms, for we are far from this goal at present. There are certain phases of the discussion which have been particularly interesting to me. A clear insight into the tuberculin reaction is essential, since the phenomena which underlie this reaction control the anatomic changes and symptomatology of the disease. Upon an understanding of it depends our knowledge both of resistance and of hypersusceptibility to the bacillus and its products. The relation of hypersusceptibility to immunity is as yet unexplained and is indeed a puzzling paradox. I have attempted to approach the subject, one might say, by a by-path and I have selected for study the immunological phenomena produced by use of readily recognizable protein substances.

Hypersusceptibility is a phenomenon which occurs in a number of diseases other than tuberculosis; the typhoidin and luetin reactions being similar manifestations. Furthermore, there is a close similarity between the tuberculin reaction and the reaction produced by sensitization with protein substances. This reaction to protein is best known

as the Arthus phenomenon. Like the tuberculin reaction it is not limited to the skin but is exhibited by tissue of internal organs as well. An acute inflammatory reaction follows reinjection after an antigen, such as horse serum or egg white, has been repeatedly injected into an animal, preferably the rabbit. At first there is no more reaction than with tuberculin given to a normal animal, but after five or six injections there is intense inflammation with necrosis, and this reaction will occur when the substance is injected into the lung or the peritoneal cavity, or the skin, but is most characteristic when injection is made into the skin in certain places. There are some differences between the action of foreign protein and that of tuberculin. The former, acting as an antigen, sensitizes the tissues, whereas tuberculin fails to sensitize although it elicits the reaction. This relationship has an important bearing upon the discussion concerning the protein nature of tuberculin. Furthermore, these studies concerning the relation of protein antigen to its antibodies have suggested an explanation of the paradoxical occurrence of resistance and hypersensitiveness in the immunized animal. It seems not improbable that the tissues are the site of meeting of the antigen and antibody and that the peculiar function of the tissues concerned determines the resulting changes. Following injection into the skin and many other tissues the obvious reaction is acute inflammation, as manifested by the Arthus phenomenon. The employment of crystalline egg albumin, representing, as it appears, a simple antigen has eliminated some of the confusing results which follow the use of complex mixtures, such as horse serum and egg white, and doubtless tuberculin as well.

The immune animal reacts with inflammation, which fails to occur when the same substance is introduced into a normal animal. Not only the skin but all of the tissues have acquired this power to react. It is expressed by increased permeability of blood vessels and accumulation of cells and serum containing antibodies in the situation in which they are most needed. Apparent hypersusceptibility is associated with a reaction which tends to increase resistance.

DR. WHITE: I will ask Dr. Long now to respond to this.

DR. LONG: I don't know that it would be worth while for me to take up individually the many points that I have had called to my attention this afternoon. We hardly have time to do that. I will speak in general terms, and individually to the men who have made many valuable suggestions. This meeting has been of exceedingly great

value to Dr. Johnson and myself in the feeling of very warm coöperation that everybody has shown, and in the knowledge that we can depend on others for help in related lines with which we are ourselves none too familiar. In connection with that coöperation let me say that of course everybody has in his work by-products of one kind or another which he is simply unable, or the time does not permit, working up himself. Dr. Johnson has told us of really enormous quantities of pretty well purified by-products which he has collected and are available for future work. I have a large amount of material also which I can send him. He referred to pure tubercle bacilli, if we can speak of such a thing, and I have a large quantity of such microörganisms on hand. Dr. Johnson is a much better man to work those up than I am, and I shall turn that material over to him as soon as I consider it safe for him to work.

Perhaps the Committee did not understand how this pyrimidine work started. There was a time when we thought there might be a more intimate relation between glycerol and pyrimidines. Dr. Johnson's analysis disclosed pyrimidines in definite quantity, and we were able to draw some theoretical conclusions, but I don't believe now that glycerol has an important bearing on pyrimidine production.

I have made various notes on other points. I might refer to, very briefly, some of Dr. Abel's questions. There is, first of all, a vast amount of literature on various endocrine deficiencies in tuberculosis, their relationship to lime deficiency, decalcification, and so on; but I do not think many hopeful leads have been obtained. Dr. Abel's remark on diffusion I regard as very helpful. I must say that it requires beautiful technique to set up such an apparatus, but I think it would be a distinct help. The subject of capillary physiology is one that we must have some understanding of if we are ever to understand the tuberculin reaction. I do not feel well enough posted to discuss the question myself. It is fortunate that we have men like Dr. Richards who can advise us on capillary poisons. I hope the time will come when we will be able to talk in terms of definite compounds, which we are not to-day.

Dr. Zinsser's point about substitution in protein and the relation to specificity in antigen is one which we cannot afford to neglect. New groups introduced in the protein molecule affect the specificity of protein biological reactions in a remarkable way, and the suggestion has been made that this phenomenon may have an important bearing on the tuberculin reaction.

DR. WHITE: Professor Abel, before you go, have you not something further to say?

DR. ABEL: I want to say that I have been much impressed by the evidence from the whole biological side, as presented this afternoon by Dr. Opie, Dr. Zinsser and Dr. Richards. Their remarks show how enormously complicated is this whole problem. This morning we appeared to be too exclusively concerned with the biological-chemical side of the problem, and we did not sufficiently take into account its medical and pathological aspects, and I am glad to see that this Committee is looking at the question in a very broad way. After all, we must try to discover facts, and incontrovertible facts in the biological and medical fields are very important, more important for humanity perhaps than is slowly developing chemical work. I simply wish to express to all these gentlemen my appreciation of their emphasis of the medical aspects of the problem. They have absolute facts to go on, and I think these facts should be developed and elucidated in conjunction with the discoveries along chemical lines. Conjoint investigations along both lines will finally, I hope, lead to a synthesis. I am sorry, gentlemen, that I must leave this interesting conference.

DR. WHITE: Dr. Lewis, will you continue.

DR. LEWIS: I also, as does Dr. Krause, come here in the double capacity of one long interested in working at a subject, to a considerable extent working on one of the phases of it, and as a member of the Research Committee. I think we have had a great deal of valuable discussion of points of detail relating to the tuberculosis problem and the things that I could contribute further are rather definitely not chemical in the strict sense of the word. They would be an application to the general biological discussion, and I think they may well be let go by. It is tremendously encouraging to this Committee to have had so much discussion on the biological side, and the evidence that has come up in this discussion that we are all, chemists and biologists alike, really thinking more or less on the same lines, each contributing something to the question of tissue reaction and the relation of various chemical products to it, is certain to be most helpful in our future consideration of projects.

I quite agree with Dr. Opie that we must even scrutinize our terminology and fundamental conception when we speak of the tissues. Two things are involved: one is the matrix in which the reaction takes place, and the other is the reaction itself. We might go further and say there are three elements: the matrix, more or less indifferent; the chemical reaction; and the complicated existence, almost certainly essential to the

progress of the disease, of a cellular exudate more or less imperfectly organized, which exists within the matrix. We have to consider these three fundamental elements and possibly a dozen more.

DR. WHITE: Dr. Hatfield, may we hear from you?

DR. HATFIELD: I have been sitting here absorbing all sorts of ideas. I want to say from the standpoint of the National Tuberculosis Association that it seems to me that this conference has been one of the most valuable meetings that has been held, and should result in one of the most valuable contributions since the Bureau of Research was organized a few years ago. I hope it will be the forerunner of such conferences of groups interested in various phases of the subject.

Dr. White then presented for approval the conclusions of the conference, the following of which were unanimously adopted:

1. That the entrance of the National Association for the Prevention of Tuberculosis into the field of Research is approved.

2. That the plan and method of the Research Committee is a wise one and in fact the only one feasible at the present time.

3. That the problem of tuberculin is a fundamental one and should be pursued.

4. That an analysis should be made, using pure substances from the beginning, that is, one strain of tubercle bacillus, chemicals of known composition in the media, uniform containers, etc. It is recommended that the Committee immediately undertake to provide this material for its chemists.

5. That there should be established conjunction experiments between the chemists and biologists and physiologists on such phases as permeability of cells, nature of inflammatory reaction, relation of blood elements to reaction, etc.

6. That care should be taken to provide the most adequate and accurate equipment for the various associated scientific workers.

Dr. White then closed the meeting as follows: In closing the meeting I want, on behalf of the Committee, to thank you all very much; you have been most helpful to us who have a very difficult problem to face. The remarks that have been made will be sent to me, and I will send copies to each one who has made them for correction before they go into the files of the Association. I want, also, to express the appreciation of all of us who have been here to Dr. Hatfield and his associates in the Phipps Institute for acting as our hosts and for their generous hospitality.

Orville W. McMichael

1867-1924

Orville W. McMichael, of Chicago, a pioneer in tuberculosis work in the middle west, died on Thursday, October 2, 1924, at the age of 57. This brief statement marks the passing of a man who, through his capacity for leadership and his unusual personality, exerted influence in Illinois and the entire middle west during the past two decades.

McMichael had the spirit of the pioneer and the adventurer, which caused him to enlist in service at the outbreak of the Spanish-American War and which led him to Alaska in search of gold in a party made up of Rex Beach and a number of kindred souls.

Becoming interested in tuberculosis, Dr. McMichael was one of the small group of men who, with the leadership of the late Theodore B. Sachs, created and developed the Chicago Tuberculosis Institute and later paved the way for the Chicago Municipal Sanitarium and the public machinery for dealing with tuberculosis. For many years, Dr. McMichael was on the staff of the Chicago Polyclinic and in charge of the tuberculosis dispensary of that institution.

He served as a director of the National Tuberculosis Association and a member of its executive committee, and was a member of the board of the Chicago Tuberculosis Institute. Early in the history of the Illinois Tuberculosis Association, he was chairman of the executive committee and, until the time of his death, he took part in the unusual clinical work of that Association which has commanded the services of the foremost medical men of the State. While Dr. McMichael had been ill since early spring, he held a clinic in one of the rural counties just two weeks before his death.

As a physician, McMichael was an earnest student and a skilful and painstaking practitioner. As a teacher he was simple, logical and convincing. In manner he was exceptionally quiet and unassuming, and with a personal charm which endeared him to those about him. It is quite within the limits of moderation to say that he was personally the most generally beloved of all the leaders in tuberculosis work in the middle west.

Orville W. McMichael

Within a few days after his death, plans were accepted for the McMichael Memorial Pavilion at the Palmer Sanatorium at Springfield, Illinois, and it was announced that in this building there would be set aside a room for the free use of tuberculosis nurses of Illinois with whom Dr. McMichael had served for many years.

G. T. P.

CORRECTION

Through a regrettable error, there occurred a transposition of figures *3b* and *4b*, in Doctor Amberson's papers in the November, 1924, number of the REVIEW. The illustration over the legend of fig. *4b*, page 247, should stand over the legend for fig. *3b*, and *vice versa*.

THE PATHOLOGY OF ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS[1]

LEROY U. GARDNER

During the past ten years fifteen cases of pulmonary tuberculosis treated by artificial pneumothorax have come to autopsy in Saranac Lake. For statistical purposes this number is small, yet a description and discussion of the pathological conditions encountered may be of interest to both clinician and pathologist; to the former because a knowledge of anatomic alteration must always serve as a guide to further treatment, and to the latter because of the bearing of these alterations on the general problems of pulmonary pathology. German pathologists have been engaged in the study of this condition from the descriptive and experimental standpoint for many years, but their studies have led to the formation of conflicting theories purporting to explain the mechanism of the reaction of the lung to this therapeutic measure. In this communication these theories will be discussed in the light of the lesions encountered.

At autopsy the lung from a patient treated with artificial pneumothorax presents a complex picture representing the terminal stages of various pathological processes. On the one hand is the tuberculous process, usually in a far-advanced condition at the time treatment was begun, and then so altered by long-continued pressure that at death its specific nature may no longer be obvious. On the other is a series of pathological changes due solely to the effects of long-continued pressure upon the normal structures of the lung. In the study of such an organ it is of fundamental importance to differentiate between these two groups of lesions, but this is often so difficult that it has become necessary to simplify the problem by observing the effects of simple compression in the lung of the normal experimental animal. Papers by Bruns (1), (2), (3), Tomaszewski (11), and Corper, Simon and Rensch (5), report in detail their own experiments on this problem and also furnish excellent reviews of the literature. Their results may be summarized as follows: An inflammatory thickening occurs in the

[1] From the Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York.

pleura and the walls of the bronchi and blood-vessels, which in some instances may become organized to form scar-tissue. A few observers have reported, in addition, the presence of fibrosis in the alveolar walls sometimes accompanied by "desquamation of the essential epithelium." The lymphatics are variously described as dilated or compressed, but the location in the lung of such alteration is not stated. Bruns (2) has apparently established the fact that a condition of relative anaemia exists within the compressed normal lung, the capillary network of the alveoli being collapsed so that only the large vessels at the root contain much blood. Maximum compression is exerted upon the periphery of the lung, particularly in the upper lobe.

Several theories have been suggested to explain the scar-tissue formation which follows long-continued compression of the normal lung. Retained bronchial secretions have been thought to exert toxic stimulaiton of the connective tissue in the walls of the bronchi. Bruns (*loc. cit.*) believes that the mere anaemia may be responsible. Others have suggested that the presence of air in the pleural cavity provokes inflammatory reaction in the pleura and that the products of this inflammation are removed by the lymphatics to the interior of the lung, where they excite similar changes in the walls of the vessels and bronchi. Warnecke (12) thought that in the tuberculous lung lymph-stasis allows accumulation of toxic metabolic products which excite fibroblastic proliferation. In the light of so many different theories it is evident that further study of artificial pneumothorax in the normal lung is desirable.

In this series of 15 cases autopsied after treatment by artificial pneumothorax, the duration of compression varied from twenty-four hours to three years and seven months. In most instances there elapsed between the cessation of treatment and the death of the patient a considerable interval of time which varied from one month to eight years. During this period some reëxpansion of the lung occurred, but in many instances the development of an exudate in the pleural cavity continued to maintain a certain degree of compression. Usually negative pressures only were employed to secure collapse of the lung, but in two cases positive manometric readings were regularly recorded. In one case they attained a maximum of +18 to +25. Three lungs of the series had been maintained in collapse by surgical procedure. In ten cases the degree of compression had been ascertained with considerable accuracy by radiographic examination.

The varying degree of tuberculous involvement in these lungs has made classification difficult. In general, there is no apparent correlation between the degree of compression and the pathological changes induced, but the duration of collapse is a more pertinent factor. Lungs maintained under moderate pressure for prolonged periods exhibit more extensive pathological change than those in which high pressures have been employed for shorter periods.

GROSS PATHOLOGY

Examination of the thorax in cases in which good compression has been obtained presents a characteristic picture. The lung, greatly reduced in size, occupies a small space in the paravertebral gutter. It is dark reddish-blue in color, and when no complicating empyema exists it presents a smooth and glistening pleural surface. Interlobar fissures are obliterated. Compression may be uniform, or the presence of adhesions to the parietal wall may prevent collapse of certain portions, resulting in the formation of thick finger-like processes projecting from the central mass to the parietal wall. Section reveals a much thickened leathery pleura, from which extend into the lung bands of similar character, representing fibrosis in the interlobular septa. The larger pleural adhesions usually enclose a considerable amount of compressed and altered lung tissue. The parenchyma of the lung is a homogeneous grey or black mass of flesh-like consistence, in which no finer air spaces are visible. Traversing it are tortuous vascular and bronchial trunks, the walls of which have been converted into dense fibrous tissue. Elongated bronchiectatic dilatations, filled with solid caseous matter or semifluid exudate, are common. Patches of calcification are scattered throughout the parenchyma. Coal pigment is deposited diffusely, and in heavier collections at the bifurcations of the trunks where lymphoid tissue is normally found.

The development of pleural effusion affects the picture only to the extent that more surface adhesions are formed and that greater thickening of the pleura results. Such changes, to some degree, influence reëxpansion after discontinuing treatment. In cases of incomplete collapse or in those in which reëxpansion has occurred, some fibrosis is present, but it is possible to recognize patches of air-containing tissue.

The alterations produced by surgical compression of the lung (thoracoplasty) in every way resemble those following artificial pneumo-

thorax with the exception of a more extensive pleural reaction. Not only is there a very heavy and irregular fibrosis in the pleura, but large irregular plaques of ossification follow the regeneration of bone from the costal periosteum.

MICROSCOPIC PATHOLOGY

From a well-compressed lung it is possible to prepare thick transverse sections of the entire organ from hilum to pleura (fig. 1). When properly cleared and stained, such preparations are of the greatest value in localizing the pathological changes. It is possible to demonstrate the absence of air-containing tissue in the peripheral two-thirds of the lung, which is heavily infiltrated with lymphoid cells and shows excessive deposition of coal pigment. Toward the hilum the much thickened vascular and bronchial trunks traverse irregularly dilated air-spaces. By this means it also becomes possible to study the condition of the lymphatics and the distribution of the tuberculous process. The former are greatly dilated at the periphery, but in the more central areas they cannot be detected.

Examination of thin microscopic sections substantiates the gross observations and adds further information; but even here it is often most difficult to determine whether a given change is solely the result of an altered tuberculous process, or of compression of previously normal structures, or a combination of both. The following changes are presumably due to prolonged pressure upon normal structures: The walls of noncartilaginous air-spaces in areas of extreme compression are obliterated and apparently fused, but in sections stained for elastic tissue the original outlines are still discernible (fig. 2). Connective-tissue stains of such areas show an apparent increase in collagen fibrils, an indicator of true fibrosis, but it should be constantly borne in mind that such a fibrosis may also be the result of healed tuberculosis (fig. 3). Where air-spaces adjoin masses of scar-tissue the lining epithelium assumes a cuboidal form, which is probably, as Borst has suggested, an adaptation to altered spacial relationships. So called "epithelial desquamation" is seen; but the epithelial origin of such intraälveolar cells is unproved, and it is not unlikely that these cells are mononuclear endothelial cells engaged in combating the tubercle bacillus.

The fibrosis in the walls of vascular and bronchial trunks, and in the pleura, is apparently preceded by the formation of granulation-tissue. In the earlier stages the loose areolar tissues in these locations are

extremely vascular, and even newly formed capillaries may be found. Gradually the tissue becomes infiltrated with plasma and lymphoid cells. Finally the blood-vessels largely disappear and the tissue becomes organized as a dense scar. It is interesting to note that these inflammatory fibroses invariably occur in tissues traversed by large lymphatic trunks, and study of sections strongly suggests that the reaction is initiated in the immediate vicinity of these trunks (figs. 6, 7, 8, 9).

As already noted, these thin-walled lymph vessels are in a state of extreme dilatation at the periphery of the lung, where other structures like the alveolar walls are completely collapsed; but at the hilum they are so compressed that they cannot be detected. Obviously, a condition of lymph-stasis induced by the compression at the root of the lung has so raised the internal pressure in the vessels that they are capable of resisting the increased intrapleural pressure. It is suggested that the collapse of the lung produces a kinking of the lymphatic trunks, where they course in the walls of the bronchi and blood-vessels from the lung to the tracheobronchial lymph nodes; and that this kinking is then followed by a stasis of the lymph peripheral to the obstruction.

The cartilaginous walls of the larger bronchi prevent compression of these tubes, but in long-standing cases bronchiectatic lesions are the rule, probably the result of the chronic inflammatory reaction in their walls. Metaplasia of the lining epithelium is not uncommon, and in several instances patches of the stratified squamous type have been observed.

Compression of the tissues results in crowding an unusual number of large blood-vessels into a unit area, but there is no actual increase in the number of vessels (fig. 4). The peripheral capillary bed is compressed, and in places obliterated, for the time being; but the thick walls of the larger arteries and veins maintain their patency. Endarteritis and thrombosis are regularly encountered in lungs long under treatment (figs. 4 and 5).

Although the series of lesions just described has been observed in lungs extensively involved by tuberculosis, it seems reasonable to believe, in the light of experimental investigations, that these changes represent the reaction of the normal structures of the lung to prolonged compression. There yet remains to be determined in how far the usual course of the *tuberculous* process has been altered by artificial pneumothorax, and whether symptomatic cure is attended by anatomic healing.

This is often a difficult matter because of the wide variation in the character of individual lesions, but here as in the study of uncomplicated tuberculosis a diagnosis of healing or progressive disease must be based upon the appearance of the majority of these lesions. The discussion of this problem is embraced under two general headings: (1) healing of original foci of disease and (2) dissemination from foci which have failed to heal.

Repair of tubercle is initiated by the prevalence of proliferative over degenerative changes. We have already observed the propensity to the formation of scar-tissue in the compressed lung, and this is manifested not only in its stroma but also at the periphery of tubercles. The latter is a location where proliferation already characterizes cell activity and the added stimulus of compression may so affect the balance that proliferation outweighs degeneration. The tubercle is replaced by scar-tissue, and what caseous matter remains becomes calcified (figs. 10, 11, 12, 13). A further possible mechanism of healing is that of resolution, for which we have experimental evidence that even caseous tubercle can heal and completely disappear (6). In sections of compressed lungs one occasionally encounters areas in which the alveolar walls are slightly thickened and which contain a few giant cells. Possibly these represent tuberculous lesions now almost healed, but the proof of resolution in such material is obviously difficult.

While individual tubercles may vary widely, the general impression derived from study of a well-compressed lung is that the majority of the lesions show a tendency to fibrosis and that calcification is more common than caseation. In other words, successful treatment is attended by a dominance of factors favoring healing. In this connection a suggestion of Bruns (*loc. cit.*) is of interest. He believes that, due to circulatory alteration in the artificially compressed lung, the tubercle bacillus no longer finds an environment favorable for continued growth. Oxygen deficiency and an excess of carbon dioxide are fatal to this microörganism. The work of Corper and his associates (4) would indicate that a concentration of carbon dioxide within the range possible under such conditions (5.5 per cent) definitely inhibits the growth of the tubercle bacillus.

Considering now the extension of the tuberculous process, it should be recalled that this can take place either directly, as a lymphatic or blood metastasis, or as the result of aspiration through the bronchi. How are these pathways influenced by compression of the lung?

Direct extension is a local invasion of the tissue spaces. The formation and contraction of scar-tissue in and about the tubercle, we believe, leads to an obliteration of these spaces. This pathway may be condsiered closed.

Lymphatic metastasis is determined by the patency of the lymph vessels and by the velocity of the lymph-flow within these vessels. If we accept the Tendeloo theory that the velocity of lymph-flow is directly proportional to the degree of respiratory movement, then this velocity must be greatly reduced in the artificially compressed lung, for the respiratory excursion is limited. In all of our cases we have demonstrated evidence of lymph-stasis. Tubercle has been found within the lumina of the lymphatic vessels, and apparently newly formed lesions of this character are encountered in the intrapulmonary lymphoid tissue, but usually such lesions are small and exhibit no caseation (fig. 18). From such evidence we are compelled to assume that the lymphatic path is open to direct extension, but that existing physical conditions eliminate it as a means of remote metastasis. Shingu (10) has demonstrated that artificial pneumothorax instituted in rabbits immediately after an intensive inhalation of soot prevents the removal of this substance to the tracheobronchial lymph nodes. Futher corroboration of the presence of lymph-stasis is to be found in clinical observation. Every practitioner who has used this therapeutic measure has observed the rapid disappearance of toxic symptoms after compression of the diseased lung, and we know that such absorption of toxic products from the tissues takes place by way of the lymph-stream.

This series does not include any case in which haematogenous metastasis is a prominent factor; but Lindblom (8) cites two instances of generalized miliary tuberculosis in which the compressed lung was spared although the opposite lung was heavily involved. The relative anaemia and the low ebb of the circulation offer convincing evidence that spread of a tuberculous process by the blood-stream must be very unusual. Experimental work on haematogenous infection in rabbits (Corper, and Tomaszewski, *loc. cit.*) has demonstrated that the pulmonary artery carries tubercle bacilli into the apparently collapsed lung with great readiness and that the microörganisms, having gained access to the organ, are retained within it because of the lymphatic obstruction. As a consequence there is as much if not more infection in the collapsed than in the normal lung. If the anatomic conditions peculiar to the rabbit's lung are recalled this apparently paradoxical condition is

explained. Miller (9) has demonstrated that in this animal the lymphoid tissue is supplied by short, relatively large branches of the pulmonary artery and, as a consequence, a large portion of bacilli introduced by way of the ear-vein are carried from the right heart through the pulmonary artery directly to this lymphoid tissue. The course of the pulmonary artery parallels that of the bronchi, and large branches are given off directly to each mass of lymphoid tissue where bifurcation occurs. The degree of compression possible to maintain does not collapse these relatively large branches because of the protection afforded by the adjacent thick-walled bronchi, and, therefore, bacilli are readily carried in large numbers to portions of the lung where infection can occur. A glance at the diagrams accompanying Miller's paper will afford convincing evidence of the plausibility of this explanation.

Opportunity for invasion of the air-passages obviously depends upon the position of the tubercle. A lesion in the well-compressed peripheral portion of the lung is not a likely source of further invasion. A tubercle in the wall of a large bronchus, on the other hand, may rupture into its lumen, with resulting aspiration and the development of pneumonic or "acinar" nodular lesions which in no way differ from those found in the uncompressed lung (fig. 15).

While, in most instances, artificial-pneumothorax treatment is followed by improvement based upon anatomic healing, this is not necessarily the case. Not infrequently the tuberculous process continues to progress and terminates fatally. In one case a "complete collapse" was maintained for one year and seven months. Before institution of treatment, disease was confined to a small portion of the upper lobe, and there was no clinical or radiographic evidence of cavitation. Injections of air were discontinued thirteen months before death and, due to the development of fluid, only slight reëxpansion occurred; yet at autopsy there was found at the apex a cavity 3.5 cm. in diameter, which the clinician believed developed during the course of collapse. In other cases severe pneumonic processes were found at autopsy in portions of the lung which were apparently uninvolved before treatment (figs. 14, 16, 17).

The clinician is interested in learning to what extent the lung is permanently damaged by long-continued pneumothorax. Animal experimentation would indicate that compression of the normal lung does not excite pathological changes which are incompatible with func-

tion. In the tuberculous lung we may assume that the ultimate result will depend upon the extent and character of preëxisting disease. The degree of fibrosis established apparently offers little resistance to re-expansion, for in fact, even in lungs long under treatment, if the injections are discontinued for a short time reëxpansion rapidly occurs and the pleural cavity becomes obliterated by adhesions.

Two cases of the series illustrate extreme conditions. One is of special interest in that a period of eight years and four months elapsed between the cessation of treatment and the time of death, which was the result of carcinoma of the ovary. The original collapse was only partial, and was maintained for a period of eight and one-half months, when the development of a pleural effusion interrupted treatment. At postmortem examination, the pleural cavity was obliterated, except for a small space over the anterolateral surface of the upper lobe. The lower lung was still partially collapsed; but some reëxpansion had occurred in the upper portions. The apex was occupied by a series of cavities, the largest 3 cm. in diameter, which were filled with dry caseous matter; there was no apparent communication with bronchi. The intervening tissue showed irregular fibrosis, but air-spaces were visible. In the lower lobe was seen an extreme grade of bronchiectasis, with much fibrosis of the trunks and parenchyma. Calcified tubercle was scattered throughout the entire lung. In spite of this extensive residual disease, the patient during the entire interval between cessation of treatment and the time of death had been free from the toxic symptoms of tuberculosis and had never been known to have tubercle bacilli in her sputum. Her only symptom was a profuse expectoration, the result of bronchiectasis. In her case artificial pneumothorax, maintained for the period of eight months, was unable to effect anatomic healing because of the extent of the previous injury.

Another patient had undergone the first stage of a thoracoplasty two years previously. A good initial collapse of the lower lobe was obtained while the upper half of the lung was only partially compressed. In spite of the collapsed chest-wall, the lower lobe gradually reëxpanded, and extension of disease continued in the upper lobe. A second operation (apicolysis) was attempted, but the patient died two weeks later. At autopsy no specific evidence of the previous collapse in the lower lobe could be found. There was some fibrosis in the pleura and the trunks, and patches of calcification were scattered throughout the parenchyma, but such changes might readily have been the result of moder-

ate uncomplicated tuberculosis. Microscopic examination demonstrated considerable fibrosis in the locations mentioned and also peripheral dilatation of the lymphatic vessels. The nontuberculous portions were otherwise apparently normal. In this case the amount of tuberculosis present in the lower lobe before compression was not sufficient to cause permanent deformity of the parenchyma, and the majority of the air-spaces were apparently capable of normal function (fig. 21).

The complications of artificial pneumothorax will not be discussed in this paper, as they do not materially affect the pathological picture. In all but three of these cases treatment was discontinued because of the development of pleural exudate. Spontaneous pneumothorax with empyema occurred six times. Extension to the opposite lung was the cause of death in two cases. This lung usually exhibits more or less compensatory hypertrophy, which was well illustrated in the long-standing case dying of ovarian carcinoma. Dilatation and hypertrophy of the right heart are said to be regular complications due to the increased resistance of the collapsed capillary bed of the lung. It was observed in only three of these cases.

CONCLUSIONS

From this study the following conclusions seem warranted:

1. Artificial pneumothorax produces the greatest compression in the outer two-thirds of the lung. Permanent anatomic alteration is dependent upon the duration of compression rather than upon the degree of pressure maintained.

2. This alteration consists in the development of a fibrosis in the pleura and connective-tissue coats of the blood-vessels and bronchi. Such a fibrosis is always accompanied by a lymph-stasis manifested by a distention of all lymphatic vessels at the periphery of the lung. We hazard the suggestion that lymph-stasis is the primary cause of the fibrosis which follows, perhaps as the result of pressure and perhaps because of retained metabolic products which afford a toxic stimulation to the areolar tissues in the vicinity of the obstructed lymph vessels. The former explanation seems more probable.

3. The blood-vessels show greatest evidence of compression in the peripheral capillary bed. Endarteritis and thrombosis are frequently encountered.

4. The beneficial therapeutic effect of artificial pneumothorax is for the most part due to an accentuation of healing in the tuberculous processes.

5. Extension of disease within the compressed lung may proceed by way of the air passages and, to a more limited degree, through the lymphatic channels. Haematogenous metastasis is probably rare.

6. The degree of permanent impairment of the lung by long-continued artificial pneumothorax is dependent upon the extent and degree of injury by the tuberculous process.

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FIG. 1. TRANSVERSE SECTION OF TWO ENTIRE LOBES AND STEM BRONCHUS

Maximum compression at periphery. Fibrosis in pleura and vascular and bronchial trunks. Large healed tubercles.

1

FIG. 2. COMPRESSED LUNG, ELASTIC-TISSUE STAIN
Thickened pleura: collapsed alveolar walls

FIG. 3. COLLAPSED ALVEOLAR WALLS, CONNECTIVE-TISSUE STAIN

2

3

FIG. 4. BLOOD-VESSELS IN COLLAPSED AREA; ENDARTERITIS

FIG. 5. LARGE VESSEL AT HILUM; ENDARTERITIS, EXUDATE IN WALLS AND LUMEN OF BRONCHUS ABOVE

4

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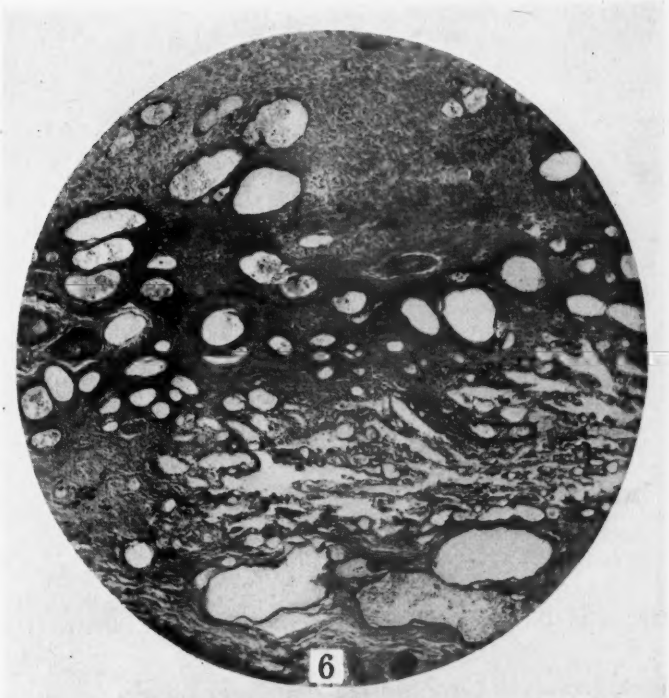
FIG. 6. THICKENED PLEURA ABOVE DARK LINE OF ELASTIC TISSUE
Below are seen dilated lymphatics in interlobular septum

FIG. 7. THICKENED PLEURA WITH ACUTE INFLAMMATION
On the right, fibrosis in interlobular septum and dilated lymphatics



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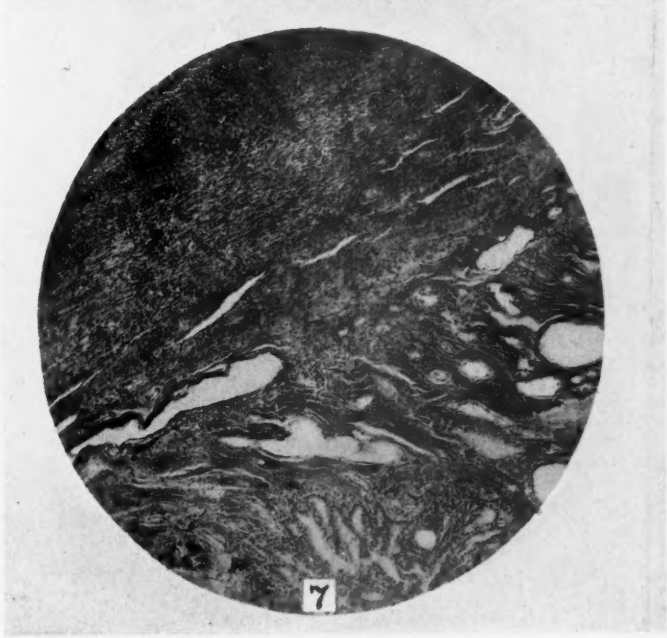

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FIG. 8. FIBROSIS IN INTERLOBULAR SEPTUM; DILATATION OF LYMPHATIC AND BLOOD-VESSELS

FIG. 9. FIBROSIS IN INTERLOBULAR SEPTUM WITH DILATED LYMPHATICS

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FIG. 10. COMPRESSED AIR-SPACES SHOWING PARTIALLY HEALED TUBERCLE

FIG. 11. HEALING TUBERCLE IN COMPRESSED LUNG

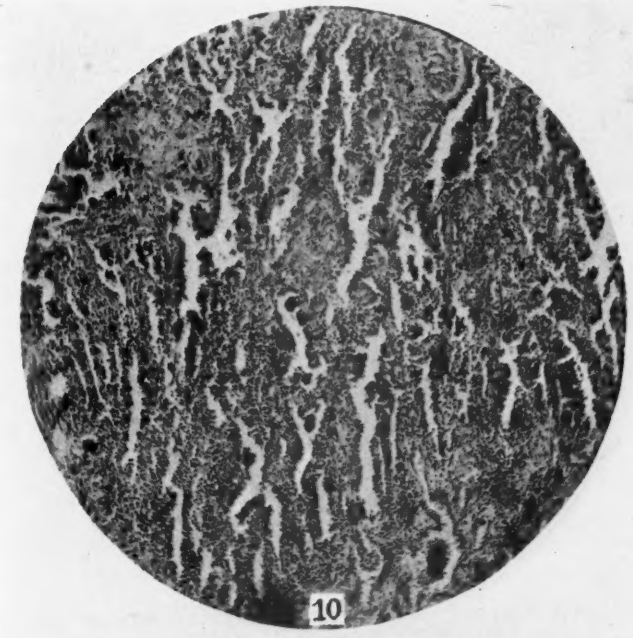

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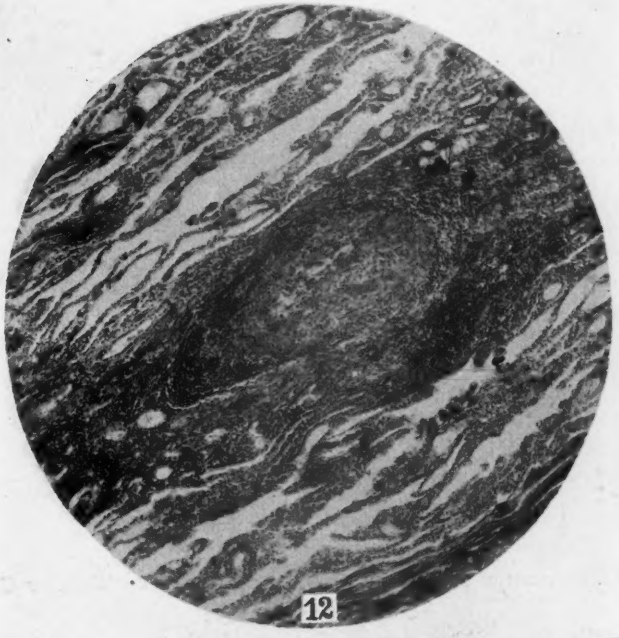
FIG. 12. LARGE TUBERCLE SURROUNDED BY INTENSE LYMPHOID INFILTRATION

FIG. 13. HEALED TUBERCLES IN LOCATION OF LYMPHOID TISSUE, ARTERIAL WALL



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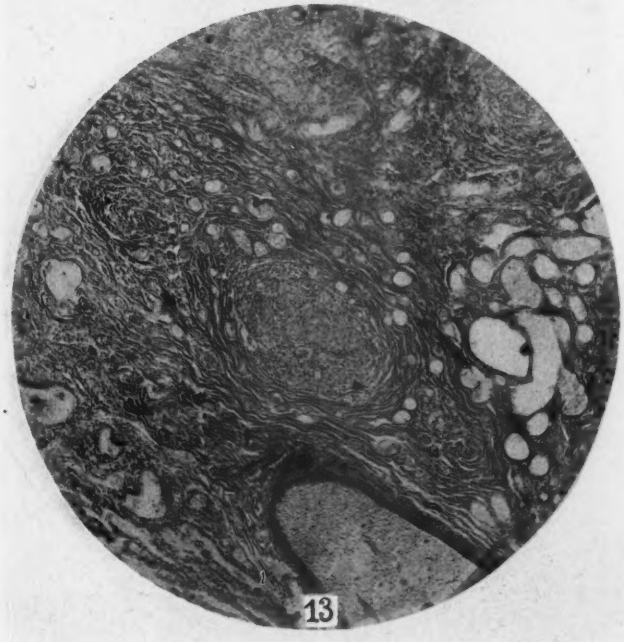

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FIG. 14. EXTENSION OF TUBERCULOUS PROCESS THROUGH WALL OF CAVITY
Lumen of cavity above

FIG. 15. INVASION OF LUMEN OF BRONCHUS BY TUBERCLE IN WALL

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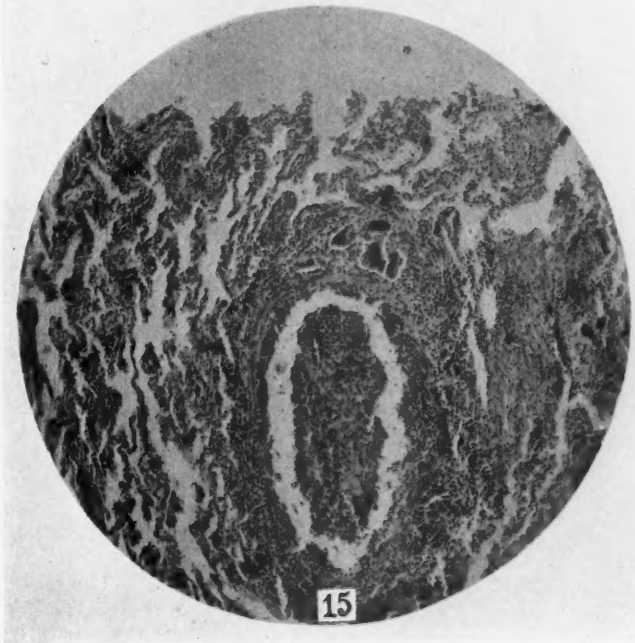

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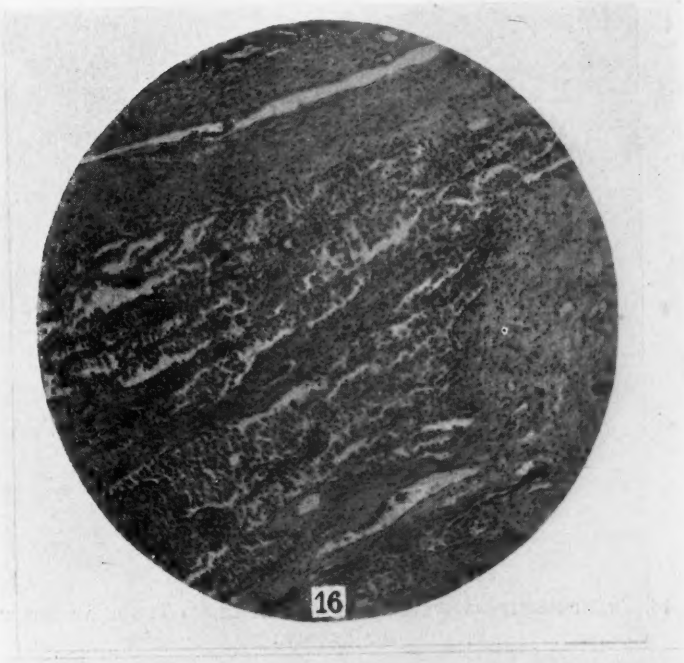
FIG. 16. EARLY PNEUMONIC REACTION IN COMPRESSED LUNG

FIG. 17. ADVANCED PNEUMONIC REACTION IN PARTIALLY COMPRESSED LUNG
Large area of caseation above



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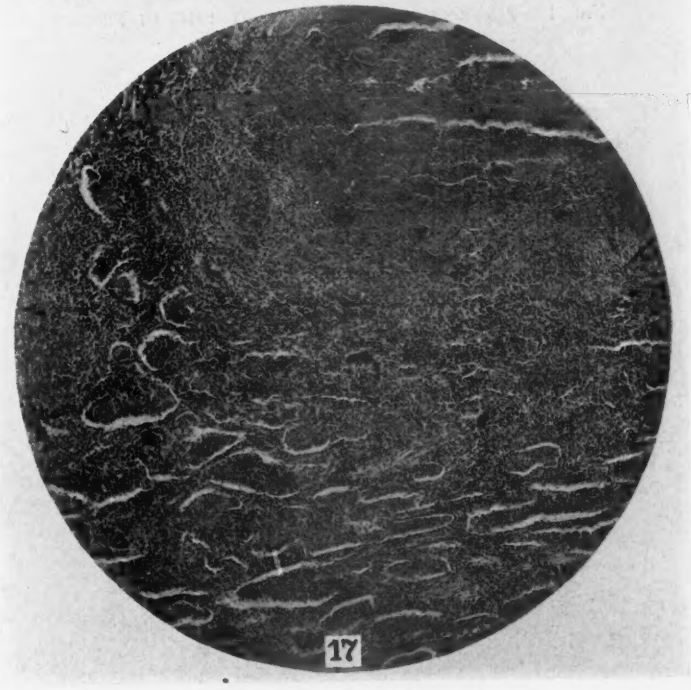

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FIG. 18. FRESH PROLIFERATIVE TUBERCLE IN LYMPHOID TISSUE AT BIFURCATION OF BRONCHI

FIG. 19. PLEURISY WITH ADHESION; FIBROSIS IN TRUNKS
Large compressed cavity

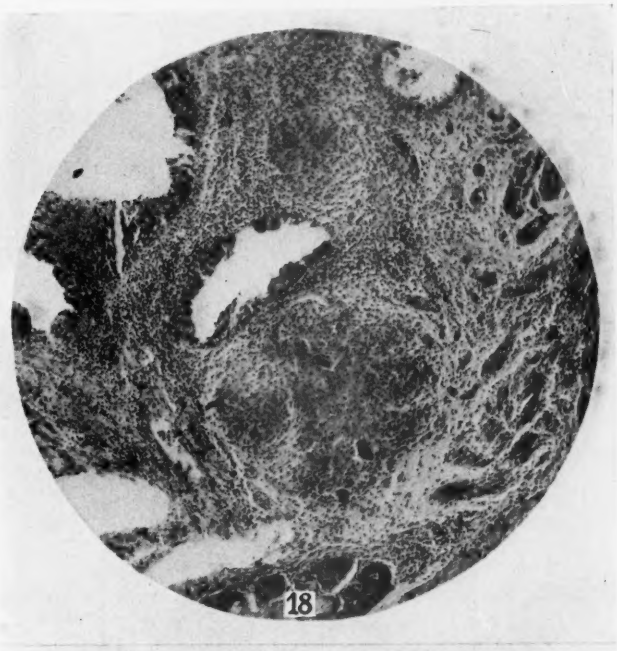

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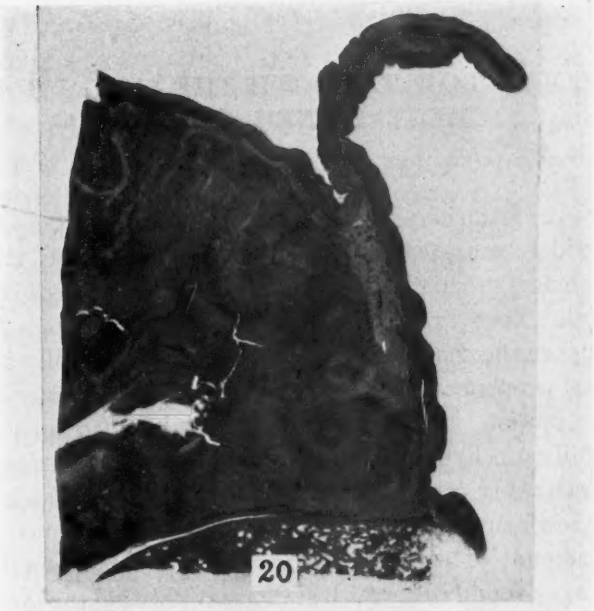
FIG. 20. THICKENED PLEURA WITH WELL-ORGANIZED ADHESION
Caseous pneumonia

FIG. 21. LUNG COMPRESSED BY THORACOPLASTY
Still compressed upper lobe with some persistent fibrosis on left; reëxpanded lower lobe on right



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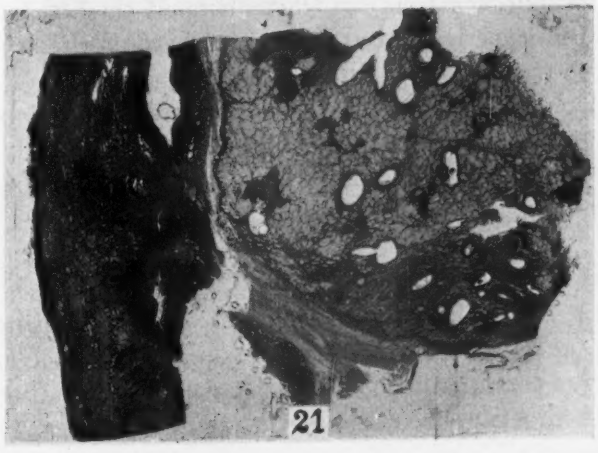

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THE BLOOD-FLOW THROUGH THE LUNGS IN EXPERIMENTAL PNEUMOTHORAX[1]

W. DOCK AND T. R. HARRISON

Although the artificial-pneumothorax treatment of pulmonary tuberculosis is a widely accepted therapeutic method, attempts to parallel its effects on clinical tuberculosis by animal experiment have been scant and unsuccessful. Even experimental analyses of the factors by which it might influence the course of the disease have been wholly inconclusive. The original proponents of the treatment considered only its effect on pulmonary motion, but later Poiseulle and Sauerbruch believed it caused significant hyperemia of the collapsed lung, while Forlanini, Brauer, Graetz and others ascribed curative value to the ischemia and lymph-stasis which they assumed to be present (1). Bruns (2), by measuring the amount of blood present in the lungs experimentally collapsed for 2 to 92 days, found ischemia, but Cloetta (3), using the same procedure and plethysmographic methods a few hours after producing collapse, found hyperemia. Corper, Simon, and Rensch (4), using the distribution of particulate matter in the lungs after intravenous injection as a criterion, concluded that the circulation through the collapsed lung was not decreased, although the results of Corper and Rensch (5) with lungs collapsed for four weeks did not wholly support the first findings. We have found no experimental or clinical evidence on the actual proportion of blood passing through the collapsed lung.

The volume-flow of blood through the collapsed and contralateral lungs of rabbits has been measured in these experiments by a simultaneous study of the oxygen consumption and the venous and arterial oxygen content.

TECHNIQUE

Rabbits of 1 to 3.5 kg. weight were used. At first urethane anesthesia was given; later this was found to be unnecessary. The oxygen consumption was measured with a Benedict portable respiration apparatus connected with a metal box closed by a rubber diaphragm fitting snugly about the animal's neck. This was made air-tight with vaseline and

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tested for leaks in the usual way. Readings were taken every 3 minutes until they became constant, and then for 30 to 90-minute periods, while blood samples were collected. Only determinations in which there were constant readings throughout were used for calculating blood-flow. The blood was obtained from the heart with a syringe containing paraffine oil in the dead space of shaft and needle, and oxalated under oil. As a rule there was little difficulty in entering either right or left ventricle, although one must be careful not to move the needle at all after beginning to aspirate blood, as there is a possibility of obtaining mixed arterial and venous blood in so doing. When many observations were made in one experiment, 1 cc. of blood was obtained in an oiled calibrated tuberculin syringe, and transferred to the extractor without oxalating. The oxygen content was determined by the method of Van Slyke and Stadie (6), and the content after aeration by the method of Lundsgaard (7). The arterial oxygen content of these animals, breathing pure oxygen from the spirometer, was found to be the same as the content of the blood after aeration in the control experiments. Such experiments also showed constant arterial and venous oxygen contents over 90-minute periods. Pneumothorax of the right side was produced, measuring the pressure with a water manometer. Six animals died shortly after having pneumothorax induced. None of them had had pressures of more than 0 to +20 (all pressures are in millimetres of water, the first figure for inspiration, the second for expiration). In these animals we found air in the left pleural cavity and a tear in the mediastinum just ventral to the inferior vena cava.

The total volume-flow may be calculated from the oxygen consumption per minute and the amount of oxygen absorbed by 1 cc. of blood in changing from the venous to the arterial oxygen content (Fick; Grehant and Quinquaud; Zunst and Hagemann, quoted by Tigerstedt (8)). Thus the volume flow per minute (tables 1 and 2) is determined by dividing the number of cubic centimetres of oxygen absorbed by the animal per minute by the difference in oxygen content of the venous and arterial blood. This implies that all of the oxygen absorbed has been taken up by the venous blood changing to arterial in the lungs, an assumption which is justified by Evans's experimental proof (9) that the oxygen used by the lung tissue is negligible.

With unilateral pneumothorax no oxygen is absorbed by the blood passing through the collapsed lung. This must be so after the first few minutes during which the air in the unexpanded tissues comes into equilib-

rium with the venous blood. All the oxygen absorption must therefore take place in the normal lung, and we can calculate the rate of flow through this lung by the method just described. Under these circumstances, the blood in the left ventricle is a mixture of blood from both the aerated and the unaerated lungs. Its oxygen content can be used only in the calculation of the total blood-flow, and for the flow through the normal lung we divide the oxygen absorbed per minute by the difference in oxygen content of venous and of aerated blood. We assume that the blood from the normal lung has the same oxygen content as aerated venous blood, because the control experiments with both lungs normal (and the animals, as in all the determinations, breathing pure oxygen) showed the arterial oxygen content and the content of aerated venous blood to be the same. The flow through the collapsed lung will be the total flow less the flow through the normal lung. For convenience our results are expressed in flow per 100 gm. body weight.

Protocols

The results of control experiments are given in table 1.

Rabbit 3: 1500 gm. Urethane anesthesia. Arterial oxygen and content after aeration, both 0.185 cc. per cc. The pressure in the right chest was brought to −8 and +10. In 20 minutes, arterial oxygen 0.165 cc.; in 40 minutes, 0.158 cc. per cc. The oxygen utilization was inconstant, and no attempt was made to calculate the flow. The fall in arterial oxygen content shows that a large amount of blood must have been flowing through the unaerated lung.

Rabbit 4: 1440 gm. Urethane anesthesia. Pressure in the right chest brought to −6 and +12. The arterial oxygen content and the oxygen consumption were inconstant during the first hour, but constant during the second (table 2).

Rabbit 13: 1800 gm. Pressure in the right chest brought to −10 and +22. Oxygen content of the blood, and oxygen utilization became constant after two hours (table 2).

At autopsy immediately after these determinations, none of the rabbits had complete atelectasis of the collapsed lung, which was still pink and crepitant although much smaller than the contralateral lung.

The Effect of Sustained Pneumothorax

Rabbit 10: 2900 gm. Pressure in the right chest adjusted to 0 and +12 to −4 and +22 daily for five days. Blood flow measured on fifth day. Immediately after, the right lung was completely airless, red and heavier than tap-water.

Rabbit 11: 3400 gm. Pressure in right chest −10 and +30 for three days. Blood-flow measured. The right lung was red, solid and airless, except for a margin of pink air-containing tissue, 5 by 1 mm., of the lower lobe.

Rabbit 12: 3200 gm. Pressure in right chest 0 and +20 to −8 and +44 for four days. Flow measured on fourth day. Right lung as in rabbit 10. In all of these animals the left lungs were unchanged.

From these protocols and from the volume-flow and blood oxygen values in table 2, it is apparent that the difference between the immediate and delayed effects are associated with the extent of atelectasis, which develops relatively slowly with pneumothorax. This is emphasized by the findings in one animal in which atelectasis was produced more rapidly. In rabbit 16, 1920 gm., the arterial oxygen content before collapse was

TABLE 1

Normal rabbits; volume-flow of blood through lungs

RABBIT NUMBER	OXYGEN ABSORBED PER MINUTE	OXYGEN CONTENT PER CUBIC CENTIMETRE		VOLUME FLOW PER 100 GM. PER MINUTE	WEIGHT
		Arterial	Venous		
	cc.	*cc.*	*cc.*	*cc.*	*gm.*
1	13.8	0.161	0.108	13.4	1,990
2	8.4	0.169	0.114	14.4	1,080
3	13.2	0.200	0.128	11.9	1,500
4	11.8	0.182	0.099	9.9	1,440
7	21.2	0.200	0.148	13.0	2,000
13	16.7	0.188	0.096	10.1	1,800
14	19.2	0.154	0.074	12.6	1,900
16	20.3	0.158	0.088	15.1	1,920

TABLE 2

Rabbits with right pneumothorax; volume-flow of blood through lungs

RABBIT NUMBER	DURATION OF PNEUMOTHORAX	OXYGEN ABSORBED PER MINUTE	OXYGEN CONTENT PER CUBIC CENTIMETRE OF BLOOD			VOLUME FLOW PER 100 GM. PER MINUTE		PROPORTION THROUGH COLLAPSED LUNG
			Arterial	Venous	Aerated	TOTAL	THROUGH COLLAPSED LUNG	
		cc.	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	*per cent of total*
4	1 hour	7.4	0.120	0.075	0.180	12.2	7.2	59
13	2 hours	15.7	0.134	0.084	0.188	17.4	9.0	52
10	5 days	22.15	0.159	0.089	0.173	10.9	1.9	18
11	3 days	28.8	0.214	0.091	0.226	6.7	0.6	9
12	4 days	32.5	0.153	0.080	0.169	13.9	2.5	18

0.158 cc. per cc. Fifteen minutes after injecting 70 cc. of paraffine oil into the right chest, the arterial oxygen content was 0.128 cc., and in 10 minutes more it had risen to 0.149 cc., showing that the amount of blood passing through the unaerated lung was about the same as in rabbits 10 and 12 (table 2). It was killed, and the right lung was completely atelectatic, red and airless.

DISCUSSION

It is obvious that the blood passing through a lung which is unable to expand will take up no more oxygen after it has absorbed that present in the alveoli at the time fixation occurs. In pneumothorax the blood in the left ventricle will be a mixture of the blood which has taken up oxygen in the normal lung and blood of a purely venous character from the collapsed lung. The exact decrease in the oxygen content of the arterial blood due to such admixture will depend on the proportion of the total blood-flow which passes through the unaerated lung. In our experiments, there has been a marked decrease in the arterial oxygen only during the period of time shortly after initiating collapse, when atelectasis is not yet complete. When collapse has been maintained for several days, or compression made more rapid by injecting paraffine oil, atelectasis is complete and the arterial blood is found to have only a slight decrease in oxygen content. Calculating the proportion of blood passing through the collapsed lung from such data, we find that within the first few hours after injecting air into a pleural cavity, 52 to 58 per cent of the total flow passes through the compressed (right) lung. Within three days this proportion falls to 9 to 18 per cent of the total volume-flow.

Our findings thus explain the apparently contradictory results of Bruns and of Cloetta, since the latter found an increase in the amount of blood contained in the collapsed lung in immediate experiments, the former a decrease in animals with sustained pneumothorax. The correlation between these findings in rabbits and the condition in man can be made only by studying the immediate and late effects of pneumothorax on the arterial unsaturation. In pneumonia Stadie (10) showed that cyanosis appeared whenever the arterial unsaturation was more than 10 per cent of the oxygen content after aeration, and occasionally with only 7 per cent unsaturation. The unsaturation of the arterial blood in our animals, when one-fifth or less of the total flow passed through the collapsed lung, was between 7 and 9 per cent. Clinically cyanosis is not an outstanding feature in pneumothorax, so we feel justified in concluding that in man the flow through a collapsed lung is greatly diminished.

SUMMARY

The volume-flow of blood in normal rabbits, as determined from the oxygen consumption, and the arterial and venous oxygen content, varies between 10 and 15 cc. per 100 gm. of body weight.

Collapse of the right lung does not greatly affect the total volume-flow, but causes a decrease in the arterial oxygen content, due to mixture of blood from the normal lung with blood of venous character which passes through the unaerated tissues.

During the first few hours after such collapse with air, the lung does not become atelectatic and more than one-half of the total flow is through the right lung during the first two hours after collapse.

The collapsed lung becomes airless and solid within a few days of establishing a positive intrapleural pressure, and the proportion of blood passing through it falls to less than one-fifth of the total flow.

Since cyanosis is absent or slight in clinical pneumothorax, there is reason to believe that marked diminution in the flow of blood through the collapsed lung occurs in man. Hence any therapeutic value of pulmonary collapse resulting from circulatory changes in the affected lung must be ascribed to ischemia.

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THE CLASSIFICATION OF ARTIFICIAL PNEUMOTHORAX AND THE CLINICAL VALUE OF THE SEVERAL TYPES[1]

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Artificial-pneumothorax therapy in pulmonary tuberculosis has received a great impetus in the last decade, and many volumes have been written treating its mechanism and therapeutic values, yet one cannot help being surprised at the many physiological and mechanical uncertainties that still prevail in the field of pneumothorax. Indeed, the many adjectives that have appeared in the medical literature describing therapeutic pneumothoraces are so ill-defined and equivocal that they are only apt to confuse the reader as to the action and efficacy of each type of pneumothorax. The following few names will show the confusion of terms that now exists in the nomenclature: Low tension pneumothorax (1), incomplete pneumothorax (2), pneumothorax of rest, *pneumothorax de repos* (3), partial pneumothorax, selective collapse (4), *Entspannungspneumothorax*, or Gwerders pneumothorax (5), displacement pneumothorax (6), and a host of others.

No doubt, some of these pneumothoraces, when analyzed properly from the mechanical or therapeutic point of view, would prove to be the same, and could be used interchangeably or synonymously; but no proper analysis and evaluation of each one have been made and no classification has yet been arranged.

Such a classification would be particularly important for the proper statistics of pneumothorax. Phthisiologists in this country and abroad have collected statistics concerning the results of artificial pneumothorax; and while there seems to be much unanimity as to its brilliant immediate results, a great deal of discussion has taken place as to its ultimate results, and statistics are notoriously uncertain in this respect.

It would seem, however, that not much value can be attached to such statistics, since in none of them is there mention of what kind of pneumothorax was used in the particular case, or what method, technique and procedure were followed throughout. They speak of the results of ar-

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tificial pneumothorax in pulmonary tuberculosis, but this is incorrect: they should speak of *pneumothoraces*, since each and every different therapeutic pneumothorax has an altogether different effect on the pulmonary tissue. Statistics, then, should be classified according to the type of pneumothorax used, and indicate which kind has achieved greater success; otherwise all the statistics collected so far have very little significance, because they try to compare altogether unequal elements.

It is the purpose of this article to classify artificial pneumothoraces according to biophysical principles and laws, and indicate as concisely as possible their corresponding therapeutic value.

CLASSIFICATION OF THERAPEUTIC PNEUMOTHORACES BASED ON BIOPHYSICAL LAWS

The mechanism of lung ventilation brought about by inspiration and expiration is well known to every medical student and to discuss this subject anew would be superfluous. However, it is important to remember that the leading rôle in contraction and expansion of the lung is played by the innate elasticity of the lung tissue itself, and that the other factors, such as the diaphragm, the intercostal muscles, the ribs, as well as the atmospheric pressure, bring about changes which allow this elasticity of the lung the greatest play.

This natural elasticity of the lung tissue can be attenuated, inhibited, injured or entirely destroyed by intrapulmonary conditions, such as infiltration of the lung tissue, stoppage of the pulmonary circulation, etc., or extrapulmonary causes due to effusion, pneumothorax and the like; the degree, extent and permanency of injury varying with the cause which produced it. It must also be kept in mind that the *contractile force* of the elastic fibres may be diminished more than the *expansile force* by certain mechanical or pathological conditions, while another cause may affect more the *expansibility* than the *contractility*, or both may be affected to the same degree. A few illustrations will elucidate the subject.

In atelectasis of short duration, the lung tissue becomes accustomed to its collasped condition, and it requires forceful deep inspiration to expand the alveoli concerned. In this condition the contractility is normal, but the *expansibility* becomes attenuated functionally to a mild degree, and can be restored by proper breathing. However, the longer such tissue is kept collapsed, the more it loses its power of dilatation, particularly when the cause is an extrapulmonary one, such as compression

by fluid or pneumothorax; and the tissue may eventually lose all its power of expansion; that is, contractility is present, but expansibility is lost.

In hypertrophic emphysema the walls of the alveoli become overdistended and their *contractile power* is much diminished, as is well known to every pathologist and clinician. This emphysema is pathological, and should not be confused with compensatory emphysema, in which, though the walls of the alveoli are distended more than normal, their nutrition is not interfered with, or is perhaps even bettered by the hyperemia, and the contractile force is almost within normal limits.

When the pulmonary tissue becomes only slightly invaded, its elasticity is attenuated, but expansibility is much more affected than contractility; and it is a well known fact that infiltrated long tissue tends to collapse and not to distend. When lung tissue, through the long process of destruction and repair, becomes fibrosed, it is hard and unyielding, and loses its elasticity completely, both as to expansibility and contractability.

With an understanding of these fundamental principles, let us turn to the study of the effect of pneumothorax on normal lung tissue. The anatomically and physiologically normal lungs hang freely in the vacuum of the air-tight thoracic cavity, and the negative intrapleural pressure allows the lung to be always stretched by force of the atmospheric pressure, to which the alveolar surface is subjected. This stretched lung tends to collapse, but cannot do so because it is unable to overcome the negative intrapleural pressure. To paraphrase this statement we can say that the intrapleural pressure and the contractile power of the stretched elastic lung are two *equal* but *antagonistic forces*. Anything which removes the negative pressure in the pleural sac will permit the elastic lung to recoil on itself, this recoil being directly proportional to the rise in the intrapleural pressure.

It is obvious enough that by introducing small quantities of air into the pleural cavity, we do not actually compress the lung, but simply remove the natural tie which holds the visceral and parietal pleurae close together, that is, the negative intrapleural pressure, and the lung simply satisfies its own elasticity and *collapses* itself, but still remains greatly expanded. This expansion bears a definite ratio to the difference in pressure existing in the pleural sac and in the lung. When the intrapleural pressure equals the intrapulmonary pressure, that is, when both are at atmospheric pressure, the expansibility and contractability of the

elastic fibres of the lung tissue are equalized, and the lung is then in a state of complete rest. If we increase the intrapleural pressure and render it positive, that is, above the atmospheric pressure, we do not only inhibit the expansile power of the elastic tissue, but actually compress it and we impart to the lung, as it were, simply a reverse physiological function. Normally, the lungs are stretched and tend to collapse; in a positive pneumothrax the lungs are compressed and tend to expand, and will do so any time the pressure is lessened by virtue of the same intrinsic elasticity, provided it has not been injured by the continuous collapse.

When we look at the action of the pneumothorax from this point of view, it will be obvious that we have to deal with three distinct types of pneumothoraces.

(*1*) When the intrapleural pressure remains negative after the inflation, say at about -10, -2 water manometer, the lung becomes slightly collapsed, the retraction being simply that of the natural elasticity, but it still possesses a great deal of its expansibility, and such a lung will dilate more or less with each inspiration. Consequently the name *expansile pneumothorax* is as descriptive as it is correct. (See figs. 1 and 2.)

(*2*) When more air is introduced into the pleural cavity, equalizing the intrapleural to that of the atmospheric pressure, the contractile and expansile forces are neutralized, and the lung is neither overstretched nor overcompressed, but is in a state of perfect rest; hence the name *pneumothorax of rest* or *static pneumothorax*. (See figs. 3 and 4.)

(*3*) When the intrapleural pressure exceeds that of the atmospheric pressure, pulmonary compression is superadded to that of pulmonary rest. It is being, so to speak, overcontracted. Such lung is perhaps put at a greater rest, but its capacity of air is reduced to a minimum, and it is greatly modified in size, shape, volume and circulation. In fact, its entire physiology is altogether changed. Its expansibility has no more chance to exert itself and it is found in a state of permanent contraction. Therefore the name *compression pneumothorax* would be very adequate for such a condition. (See figs. 5 and 6.)

FIGS. 1 AND 2. EXPANSILE PNEUMOTHORAX

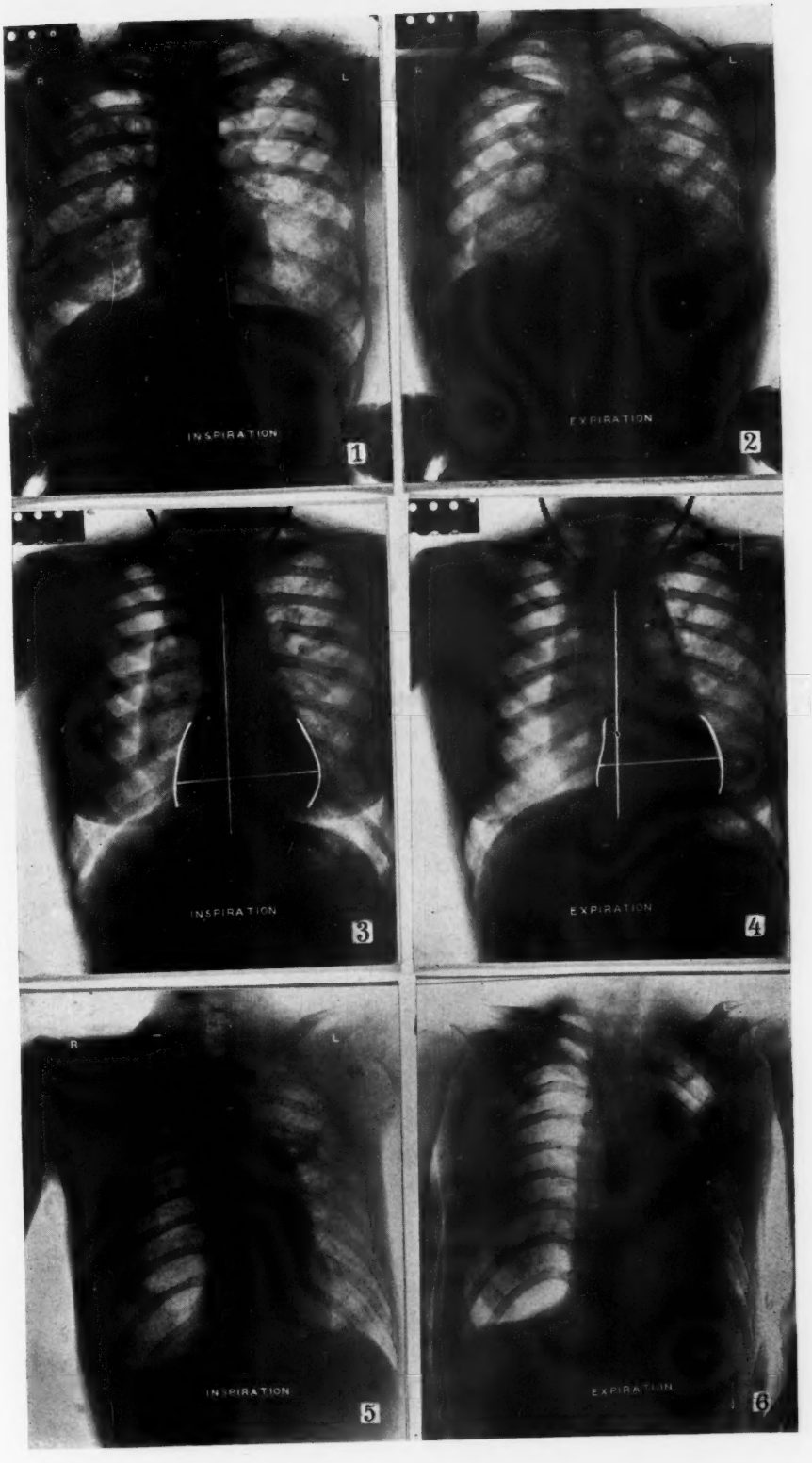
Plates taken in inspiration and expiration, respectively. Show the right middle and basal lobes dilate to almost their full capacity during inspiration and contract to almost half their volume during expiration, whereas the diseased upper lobe remains in the same form and position during both respiratory phases. The inspiratory and expiratory intrapleural pressures are both negative and the mediastinum is therefore affected by the respiratory movements only to a very limited extent.

FIGS. 3 AND 4. PNEUMOTHORAX AT REST

Plates taken in inspiration and expiration, respectively. Show that the right collapsed lung neither expands nor contracts with the respiratory phase. The hardly perceptible motion *en masse* of the entire lung is due to the movement of the contiguous organs, particularly that of the mediastinum, which is labile in this case and exhibits a to-and-fro swinging, being pushed toward the contralateral side during expiration because of the positive expiratory intrapleural pressure.

FIGS. 5 AND 6. COMPRESSION PNEUMOTHORAX

Plates taken in inspiration and expiration, respectively, of a case of a right spontaneous pneumothorax, in which both the expiratory and inspiratory intrapleural pressures were highly positive (only after the aspiration of 1000 cc. from the pleural cavity did the inspiratory pressure become slightly negative). The compressed lung is seen hung up near the upper mediastinum in the form of a small pear. The mediastinum in this case is very labile, and even during inspiration it is displaced toward the contralateral side, reaching the nipple line during expiration.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THE INTERDEPENDENCE OF HEMODYNAMICS AND PNEUMODYNAMICS, AND HOW AFFECTED BY EACH TYPE OF PNEUMOTHORAX

While we direct most of our attention to pneumodynamics in pneumothorax treatment, we forget that a knowledge of the changes in the hemodynamics resulting from the collapse of the lung is just as important for the immediate as well as the ultimate successful outcome of this therapy.

To quote Yates (7),

> Indeed, so intimate is the interdependence of respiration and intraplumonary circulation that the degree of integrity of the pulmonary circulation, compared to normal, directly or indirectly measures not alone intrathoracic conditions, but also pleural and pulmonary powers of defense and repair. Consequently the evaluation of intrathoracic therapeutic procedures can be estimated by protection and rehabilitation assured to the lesser circulation.

It goes without saying that the competency of the circulation in the treated lung will be inversely proportional to the deflation of the lung, and that, the more we collapse it, the more we diminish the volume of the blood of that lung.

In the *expansile* type of *pneumothorax* in which the intrapleural pressure is always below zero and the deflation of the uninvolved portion of the lung is only partial, the lesser circulation, as well as the bronchial arterial blood supply, is affected only slightly. Futhermore, this circulation, though diminished, acquires a greater velocity, since the same amount of blood passes through a lessened bed; consequently the absorption of the intraälveolar air is more rapid, and the result is a more efficient ventilation of the lung.

In the *pneumothorax of rest* in which the pressure is at zero, the calibre of the pulmonary blood-vessels is greatly reduced, offering great resistance to the ingress of the blood, but still, with proper compensation of the right ventricle, this obstacle may be overcome, and an adequate circulation will be maintained even in the collapsed lung, and thus avoid the formation of permanent atelectasis and atrophy of the lung tissue.

In *compression pneumothorax*, in which the intrapleural pressure is above zero and the tension invariably surpasses that of the intravascular tension, the blood-vessels become constricted or obstructed altogether, and even with an adequate power of cardiac compensation a very small volume of blood is driven through this lung.

This compensation of the heart is definitely shown by the cardiac enlargement after the first few inflations, as well as by the rise in the systemic blood pressure after each of the first inflations. Whether the en-

largement is due to hypertrophy and dilatation of the heart, or only to hypertrophy of the cardiac muscle, we are not ready to state; but the fact is that there occurs a decided enlargement of the heart, particularly in the right ventricle. Measurements of the transverse diameter of the heart before the initiation of pneumothorax, and a few weeks afterward, exhibit a definite increase in the transverse diameter, as shown in figs. 7, 8, 9 and 10.

This hypertrophy of the right ventricle which invariably takes place in every case treated with pneumothorax, provided the reserve energy of the myocardium has not yet been exhausted and it is able to come into action at any time demand is made upon it, is no doubt the result of the much increased work which it has to perform, propelling the blood against a higher and additional resistance, not only in the compressed lung but also in the contralateral one, through which a much greater volume of blood is to pass *per same unit of time* in order to keep both the systemic and the pulmonary circulations in equilibrium.

Without going into detail it may be stated that, on the whole, the same quantity of blood must pass per unit of time through the lesser circulation as through the greater circulation; otherwise equilibrium cannot exist, and blood would accumulate either in the lungs or in the systemic vessels. Now when we reduce the bed for the blood-flow in one lung, and when the intrathoracic pressure exceeds the intravascular tension of the pulmonary blood-vessels, thus compressing them, the blood-stream is immediately diverted to the other lung, which offers much less resistance. Since, however, the blood-vascular bed in the undeflated lung is too small to contain this increased amount of blood (this increase of the quantity of blood bearing no doubt a direct relation to the degree of the diminution of blood-vascular area in the pneumothorax lung), it offers at first great resistance, and the pressure rises. But, as explained above, the right ventricle compensates, and its contraction becomes stronger, until it overcomes the resistance in the lung, in which a dilatation of the blood-vessels occurs. It is this dilatation of the blood-vessels, as well as the greater quantity of blood in that lung plus the compensatory emphysema, that imparts a peculiar haziness to the skiagram of the untreated lung in the first weeks of pneumothorax treatment. (Compare figs. 9 and 10, and 7 and 8.)

The rôle of the compensatory emphysema of the contralateral lung, as well as in the homolateral lung in expansile pneumothorax, and its effect on the course and the result of the treatment, will be discussed in

FIG. 7. PLATE TAKEN THREE DAYS BEFORE INDUCTION OF PNEUMOTHORAX

Note the infiltration and small cavitation in the middle lobe and upper portion of basal lobe of right lung.

FIG. 8. PLATE OF SAME PATIENT AS OF FIGURE 7, TAKEN SIX WEEKS AFTER THE INDUCTION OF RIGHT PNEUMOTHORAX

Note that the uninvolved parts of the lung expand much more than the involved portions. (Inspiratory and expiratory intrapleural pressures were both left below zero.) Note particularly the increase of the transverse diameter of the heart. There is almost no displacement of the mediastinum.

FIG. 9. PLATE TAKEN A FEW DAYS BEFORE INDUCTION OF PNEUMOTHORAX

Note the marked confluent infiltration of left lung and haziness of its lower basal field

FIG. 10. PLATE OF SAME PATIENT AS OF FIGURE 9, TAKEN SEVERAL WEEKS AFTER INDUCTION OF LEFT PNEUMOTHORAX

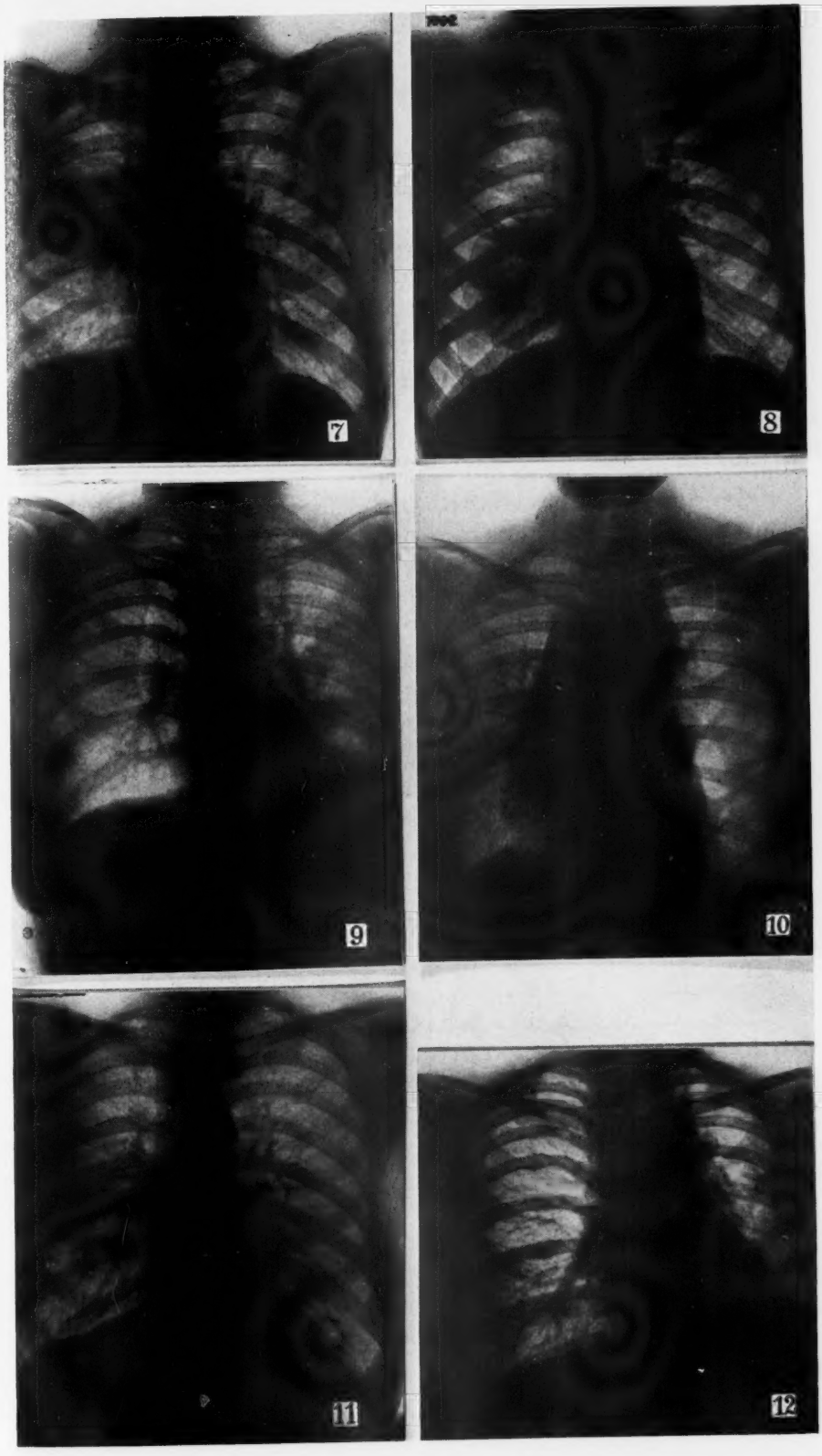
Note the marked compression of entire left lung. (The intrapleural pressures were positive.) Note particularly the marked displacement of the mediastinal structures to the right and the considerable increase of the transverse diameter of the heart. The right lung appears hazy, due to compression and hyperemia.

FIG. 11. PLATE OF SAME PATIENT AS OF FIGURES 7 AND 8, TAKEN SIX MONTHS AFTER THE TERMINATION OF PNEUMOTHORAX TREATMENT

Note the marked compensatory emphysema of the upper and lower lobes of right lung as well as of left lung. There is only a slight accentuation of lung markings and root changes of right lung. The transverse diameter of the heart is the same as before the application of pneumothorax. Note particularly the equipoise of the mediastinum.

FIG. 12. PLATE OF SAME PATIENT AS OF FIGURES 9 AND 10, TAKEN ONE YEAR AFTER THE TERMINATION OF PNEUMOTHORAX TREATMENT

Note the marked narrowing of the left hemithorax, the considerable distortion and pulling of all the mediastinal structures to the left side, the apex of the heart reaching the thoracic wall.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detail in a later article. Suffice it to say, that without the development of the compensatory emphysema respiratory distress in pneumothorax cases would be unavoidable.

As mentioned previously, we also observed that the blood pressure rises after each of the first few insufflations from 20 to 40 mm. Hg. in systole and 15 to 25 mm. in diastole. The subsequent reinsufflations do not change the blood pressure materially, though the blood pressure seems, as a whole, slightly higher than before the treatment was commenced.

We have also noticed that there is almost invariably an increase in the hemoglobin (10–25 per cent) and in the red-blood cells (5000 to 1,000,000) during the first few weeks of treatment.

These sphygmomanometric changes resulting from the deflation of one lung, as well as the relative polycythemia and the increase in the hemoglobin, need further investigation, and corroboration through experimentation on animals, and will be reported subsequently.

Whatever the explanation may be, the fact remains that the modification in the hemodynamics is consequential to the alteration in the pneumodynamics, and the successful result of the treatment depends a great deal on the adequacy of the compensation of the circulatory system, and its close observation during the course of pneumothorax treatment may be a great help in prognosticating the success or failure of the case.

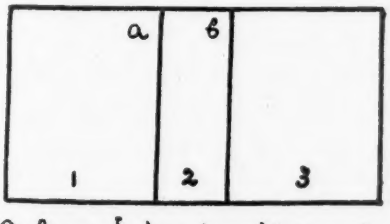
It goes without saying that the demand on compensatory changes of the circulatory system is greater and much more exigent in compression pneumothorax than in the pneumothorax of rest, and is less urgent and more gradual in expansile pneumothorax.

RÔLE OF THE MEDIASTINUM IN EACH TYPE OF PNEUMOTHORAX

There seems to be a great lack of harmony between the observations on the intrathoracic pressures in both hemithoraces produced by unilateral artifical pneumothorax. Bell and Graham (8) report that a slight alteration in one pleural cavity is accompanied by an alteration in pressure in the other pleural cavity to almost the same extent, provided the mediastinum is mobile and no adhesions are present. Yates (9), on the contrary, reports his observations of artificial pneumothorax on various animals and came to the conclusion that "air injected into one pleural cavity of a dog will produce a bilateral decrease in the negative pressure because the mediastinum is not air-tight." But in monkeys and in man, whose mediastinum is air-tight, a positive intrapleural pres-

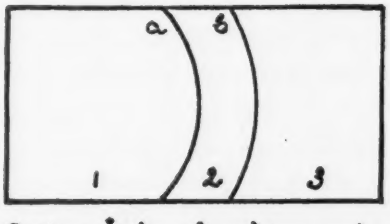
sure on one side may provoke only a slight change in the negative pressure of the contralateral pleural cavity. Matas (10) and Duval (11) seem to have had the same experience. Other investigators (12) have supported the observations of Bell and Graham, and it seems very difficult to reconcile these contradictory observations, unless we say that they experimented with different types of animals, under different conditions of the animals, and with different technique and regimen.

We are rather inclined to accept Graham's and Bell's observations, but with some reservations. While it is true that the thorax may be considered as one cavity, it must always be remembered that it is divided into three separate compartments by two elastic partitions. The three compartments are the two pleural cavities and the mediastinal space, the partitions being the two lateral walls of the mediastinum consisting of the elastic layers of the pleura. When air is introduced into one pleural cavity, it will exert an equal pressure in all directions, but the rigid wall of the thorax will be the least affected by the pressure, and the diaphragm, the less rigid, will feel the pressure but to a limited degree because the intraäbdominal tension will counterbalance it, and most of the pressure of the quantity of air introduced into the pleural cavity will therefore exert itself on the least resisting wall of the cavity, that is, on that of the mediastinum. But even this least rigid part opposes a certain resistance to distention, and so will hold off, as it were, from the mediastinal cavity a portion of the intrapleural pressure; and this "intramediastinal pressure" will be equal to the newly created intrapleural pressure minus the elastic tension of the mediastinal wall. The following diagrams (1 and 2) of a simple mechanical contrivance, consisting of an air-tight box divided into three compartments by two elastic rubber partitions, will illustrate this fundamental principle very clearly.



Before Introduction of Air.

Diagram 1



After Introduction of Air into Compartment 1.

Diagram 2

Let 1, 2 and 3 represent the right hemithorax, the mediastinum and left hemithorax, respectively; *a* being the lateral wall of the mediastinum separating it from the right pleural cavity, and *b* separating the mediastinum from the left pleural cavity. Now when we introduce a certain quantity of air into cavity *1*, it will exert most of its pressure on the least resistant wall, *a*, putting it on the stretch and pushing it into compartment *2*. The pressure then in *2* will be equal to the pressure in *1*, minus the elastic tension of *a*. Now, since the pressure in compartment *2* will be greater than in *3*, *b*, the least rigid wall of the cavity, will be distended and bulge into cavity *3*, and evidently the pressure in *3* will be equal to the pressure in *2* minus the elastic tension of *b*. It is obvious enough that the pressure varies in each compartment, and that it will be less in *3* than in *2*, and less in *2* than in *1*. Substituting this diagram for the two pleural cavities and the mediastinum, we shall have the same phenomenon. Thus the alteration of pressure in the right pleural cavity, due to the introduction of a certain amount of air, will be accompanied by a change in pressure also in the left side, which will be equal to that of the right side minus the elastic tension of both lateral walls of the mediastinum.

It should not be forgotten, however, that the pleural cavities are not empty, but contain the stretched lungs, the intraälveolar pressure of which is equal to the atmospheric pressure; consequently, another factor of resistance to the introduced air should be taken into account. Indeed, the first few hundred cubic centimetres of air introduced into the pleural cavity exert all their pressure on the stretched lung, trying to neutralize the intraälveolar atmospheric pressure in order to relieve the contractile force of the elastic lung tissue and allow it to recoil on itself. It is only when the intrapleural pressure reaches about zero that it begins to exert itself mostly on the mediastinal wall, as is so beautifully illustrated in chart 1.

At first there is a gradual rise in the intrapleural pressure with each ingress of 100 cc. of air, as shown by the decreased manometric readings in inspiration and expiration (see curve), but when the mean pressure is at about zero, there seems to be a certain relatively stationary point, at which there is no further rise in the expiratory pressure after the induction of 100 or 200 cc. of air. At this point the mediastinal wall, the least rigid of the cavity, becomes deflected and pushed into the other cavities, thus widening the transverse diameter of the insufflated pleural cavity, and consequently no perceptible increase in pressure is noticed, though

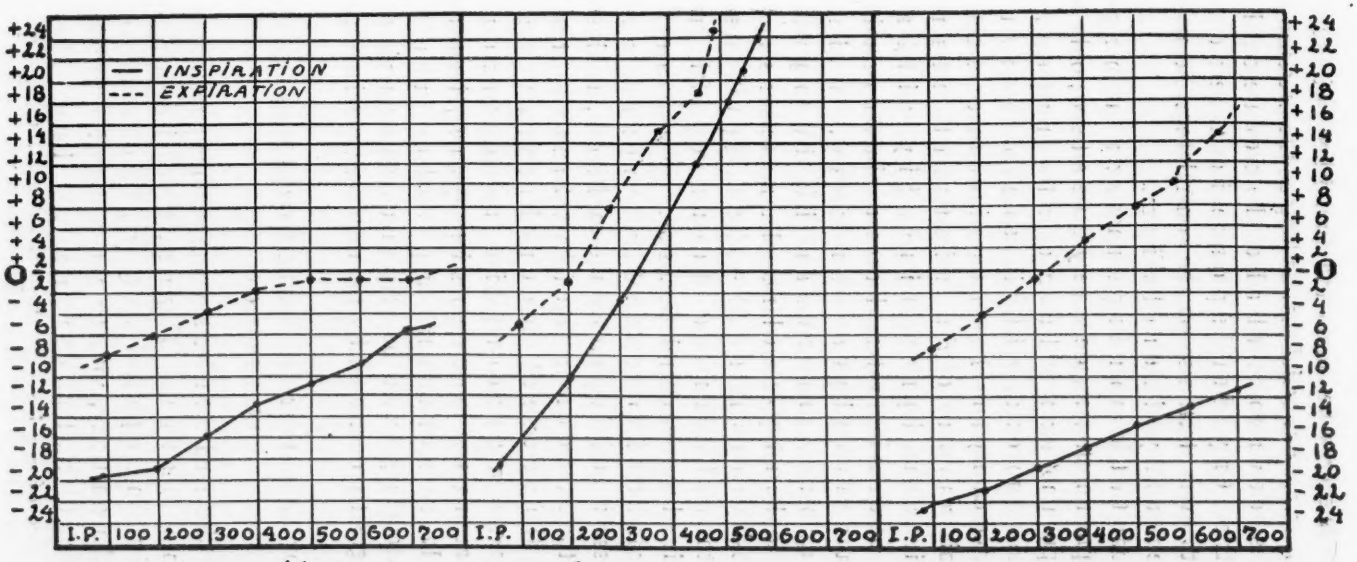


Chart 1. Labile Mediastinum with Partially Functionating Lung.

Chart 2. Rigid Mediastinum with Compressed Lung.

Chart 3. Rigid Mediastinum with Partially Functionating Lung.

The abscissae indicate the amount of air in c.c. induced into the pleural cavity. The ordinates indicate the intrapleural pressure measured by water manometer.

the other lung becomes encroached upon and diminished in its functioning surface. It is therefore our belief that as long as the pressure in the pneumothorax side is below zero, it will affect the pressure on the untreated side very little. Only when the pressure rises to zero or above that, will it begin to exert itself also on the contralateral hemithorax, depending upon the flexibility of the mediastinum.

It is obvious enough that in expansile pneumothorax the intrapleural pressure of the nonpneumothorax side is very little altered; only in the other two types of pneumothorax will changes in the intrapleural pressure of the other side be provoked, which will depend on the pressure existing in the insufflated cavity and the amount of resistance of both mediastinal walls. This resistance of the mediastinum to pressure is a very variable quantity, depending much on its elasticity, which is altered as the mediastinum becomes infiltrated, thickened, fibrosed or adherent, and different pressure relationships are then invoked. At times the mediastinal walls may become so adherent and rigid that they will offer a marked resistance to the newly created intrapleural pressures, and even such an enormous positive pressure as +30, +20 mm. Hg. will cause very slight deviation of the mediastinum and, of course, very little pressure will then be transmitted to the contralateral side. In such cases a very small quantity of air induced into the pleural cavity will result in a markedly heightened pressure, both inspiratory and expiratory, as illustrated by the sharp steep the plotted curves take (charts 2 and 3). It is needless to state that in the presence of a labile mediastinum no such high pressure could be created and no compression pneumothorax could be obtained without causing the most distressing dyspnea, inasmuch as in such cases not only the pneumothorax lung is reduced in its volume, but also the untreated lung would be very much embarrassed and its respiratory surface greatly decreased by the displaced mediastinum.

FINAL RESULTS OF EACH TYPE OF PNEUMOTHORAX AND CLINICAL CONSIDERATIONS

Thus far we have discussed the effects of the various pneumothoraces on normally functioning lung tissues. However, it is evident enough that the same amount of air in the pleural cavity will act differently on diseased lung tissue, the elasticity, vitality and histological architecture of which have been modified, than on normal lung tissue. Altogether new and different laws of statics and dynamics reign here. Thus, it

was mentioned previously that infiltrated lung tissue may lose its power of expansion and yet will retain its contractile force; in other words, the expansibility of the infiltrated lung tissue is always more impaired than the contractibility, and there is a tendency for such diseased lung tissue to undergo atelectasis. Consequently, the amount of gas in the pleural cavity below atmospheric pressure, which will only partially reduce the expansibility of the normal lung, will entirely inhibit the expansile power of the diseased part, which has already been weakened by the pathological alterations.

Furthermore, those alveoli, the tissue of which is infiltrated or even edematous and congested, contain much less air than the alveoli of normal lung tissue; and it will require *little* compression to render such areas entirely airless, so that no inflow of air into such areas will occur even on deep inspiration; this being one of the main objects of the pneumothorax, to keep the diseased alveoli from a to-and-fro motion by the ingress and egress of air. A little movement perceptible in such compressed airless areas is only a motion *en masse*, which is transmitted to it by the contiguous tissue and organs.

If the diseased part of the lung is soft or caseous, with almost no vestige of the former elastic structures of the lung tissue, a still smaller amount of air will be required to compress it, as it offers no resistance whatsoever.

On the contrary, a lesion with much fibrosis and induration will not undergo any collapse by gas or air, because it is hard and unyielding. Consequently, when air is introduced, the healthy tissue will be compressed first, and since such lesions are usually extensive the outline of the collapsed lung will be ragged and unequal throughout the skiagram.

As may be expected, the diseased portion of the lung, once it becomes collapsed, stays so through the entire course of the treatment, taking no part in the expansile mechanism of the pneumothorax. Just exactly how the healing process is augmented is not the purpose of this article to discuss, but as the tissue probably goes through all the gamut of the processes of healing and repair, it becomes more and more contracted and reduced in size, while the uninvolved portion of the same lung, the expansile part, undergoes a vicarious emphysema, and dilates step by step, until it is able to fill the entire hemithorax.

We thus see that the two processes, that is, the expansion of the functioning portion of the lung and the collapse and contraction of the diseased portion, take place simultaneously. Therefore, when we introduce a small amount of air into such a cavity, a most fascinating phe-

nomenon will be observed; the air will in about two or three days accumulate around the diseased portion, no matter where it be located,—apex, middle lobe or base. It is this phenomenon that led Barlow and Kramer to call it *Selective Collapse* (13) and which Stivelman and Hennell accepted with some reservation (14); but it seems to us that this name would be rather apt to mislead. There is no affinity of the diseased part for the air, neither is there any predilection in the air for the diseased part. It is simply a natural phenomenon explained on physicodynamic laws of displacement. The diseased, contracted part has either no respiratory movements at all or, if present, they are of a very limited range, while the movements of the functioning lung are of a large amplitude and they drive the air out, or *displace* the air, which will naturally follow the line of least resistance, that is, the empty space produced by the contraction of the diseased portion.

As we progress with the pneumothorax treatment, the expansile portion of the lung assumes almost normal respiratory function, its circulation becomes competent and physiologically compensatory emphysema begins to develop, thus expanding gradually and occupying the space that was produced by the contraction of the diseased tissue, until it fills up the entire pleural space without pulling other structures into this hemithorax, as shown in fig. 11.

There is no need to discuss again why in expansile pneumothorax the question of "when to let the collapsed lung reëxpand" does not exist at all. This complicated dilemma which has been baffling every operator of pneumothorax since the days of Forlanini, solves itself in the expansile type of pneumothorax. Expansion starts from the very first insufflation. In other words, the collapse of the diseased portion of the lung and the expansion of the uninvolved portion go hand in hand, until the expansile part has compensated enough to replace entirely the collapsed and by this time, healed tissue. At times no vestige of the old lesion can be found, even no fibrosis or scarification. (Compare figs. 7 and 11.)

It may be interesting to compare here the end-results of pneumothorax in those cases which were treated many years ago by high-tension pneumothorax, or as we would call it now by compression pneumothorax. It will be noticed from the X-ray plate that all the mediastinal structures, as well as the diaphragm, have been pulled into the treated hemithorax in order to fill up the pleural cavity (see fig. 12). This phenomenon is

well known to everyone who has dealt with pneumothorax cases, and no interpretation as to why this occurs is necessary.

A comparison of the distortion and asymmetry of this case (fig. 12) with the perfect symmetry of both hemithoraces and the resulting equipoise of mediastinum in its natural place of fig. 11 will convince any one as to the efficacy of each type of pneumothorax.

It is obvious from the foregoing that expansile pneumothorax could be used as a therapeutic measure in a much greater number of tuberculosis patients than it has hitherto been applied to. Not only is it expedient in, so to speak, classical unilateral cases, but it can also be used with great advantage in bilateral pulmonary tuberculosis cases if they are not anatomically far advanced. The fear of putting all the burden of respiration on the noncollapsed lung has no place in expansile pneumothorax, because the uninvolved portion of the treated lung continues to function all the time. Surprisingly enough, even the untreated lung shows marked improvement and a greater tendency toward healing and repair. Just what the explanation is cannot be said with certainty; but there is no doubt that the amelioration of the subjective symptoms following the creation of the pneumothorax, the lessened toxemia and the improved general well-being contribute a great deal to the process of healing. Perhaps the active hyperemia produced in the lung, if the heart compensates well, plays its share in the augmentation of healing.

It must be taken into consideration that the compensatory capacity of the heart is much greater in early cases of pulmonary tuberculosis, in which the cardiac muscles have not yet become attenuated and exhausted through long-standing toxemia, and are able to compensate more readily whenever demand is made upon them. Any pneumothorax occasions a diminished oxygenation, and to make up for it the heart activity is accelerated and increased, as is evidenced by the temporary rise in blood pressure and the dilatation of the heart in every case of pneumothorax. As was mentioned previously, expansile pneumothorax requires the least compensation of the heart; but by lessening the toxemia it brings about an improvement of the heart action which helps to ameliorate the general condition of the patient, thus increasing its power of resistance and process of repair.

Expansile pneumothorax, then, should not be considered as a last resort for desperate tuberculosis cases, but should be employed as a definite therapeutic measure in many cases of pulmonary tuberculosis, since it offers a much more effective and speedy recovery than any other

treatment that has been used until now. This treatment is strikingly effective in early cases of tuberculosis, cases which anatomically belong to stage 1 or 2, but clinically run an acute or subacute course. The immediate clinical mitigation in such cases is almost startling. All the subjective symptoms, such as pyrexia, cough and expectoration, sweats, asthenia, anorexia, etc., due to the toxins elaborated in the caseous foci, disappear within a short time after the initiation of the treatment.

At first, pneumothorax should be that of pneumothorax of rest, that is, the intrapleural pressure should be at zero or -1, water manometer, *in inspiration*, while the pressure *in expiration* should always be a slightly positive one. Patients should be watched carefully before and after each inflation, by observing the respiratory movements of each lobe of the collapsed lung. After the abatement of all the subjective symptoms the intrapleural pressure should be gradually reduced, the *expiratory* pressure in the pleural cavity remaining not higher than that of the atmospheric pressure, while the *inspiratory* intrapleural pressure should be kept negative, its negativity varying with each particular case. No generalization or standardization of pressures can be made for all cases of pneumothorax, but each case has to be individualized and studied by itself. Furthermore, even each individual case cannot be kept with the same optimum pressure all the time, inasmuch as each subsequent insufflation differs slightly from that of the previous one.

It should be kept in mind that each reinsufflation is given with the purpose of keeping only the diseased portion of the lung at rest, whereas the uninvolved part is to remain more or less unfettered in its respiratory action, and the amount of gas at each reinsufflation, as well as the intrapleural pressure, should vary accordingly, a larger amount of gas being required for a larger lesion and *vice versa*. The case should be studied stethoscopically and fluoroscopically very frequently, in order to detect any changes that take place in the lung. It is understood that the intervals of reinsufflation should be very short, at first every week and later every other week, but never longer than three weeks. Again, no definite rule of spacing the reinsufflations can be given, but each case is a study by itself, being controlled by the stethoscope, fluoroscope, and vital capacity, as well as by subjective symptoms.

As stated before, the question of when to let the lung reëxpand does not exist in expansile pneumothorax, since in this mode of treatment the expansion of the functioning portion of the lung and the contraction of the diseased portions go hand in hand; and, as was illustrated above, the

functioning portions undergo vicarious emphysema, expand gradually but persistently, and fill the space left by the healed and contracted portion. The fibrosed and cicatrized part becomes so completely surrounded by emphysematous lung tissue that very often it cannot be detected even on the skiagram.

Of course, no such results can be expected from pneumothorax applied to far-advanced cases, with extensive anatomic lesions which outmeasure the functioning portion of the lung concerned, with many fibrosed and inelastic areas here and there, and with thickened pleura and synechiae between parietal and visceral layers. In such cases a high tension must be used, in order to accomplish *compression* of the lung, but fortunately in such cases the mediastinum is usually rigid, and compression pneumothorax can be used without encroachment on the contralateral lung. But, while amelioration of the subjective symptoms and general improvement can be accomplished by compression pneumothorax, no anatomic recovery, and certainly no functional recovery, can be expected, and the pneumothorax will have to be maintained for many years, if not throughout life, in order to prevent retraction and deformity of the hemithorax.

It is evident enough that such cases should never be compared with cases treated by expansile pneumothorax, inasmuch as in the former cases the pneumothorax was the *ultimum refugium*, while in the latter it was the treatment of choice. Statistics of therapeutic pneumothorax hitherto collected have failed to take these facts into consideration, and to judge the efficacy of pneumothorax treatments on pulmonary tuberculosis by including all the far-advanced and desperate cases, which were doomed to death anyhow, would be incorrect and unfair, just as it would be unfair to draw conclusions on the efficacy of the surgical treatment of appendicitis by including all neglected cases of ruptured appendices with those of general peritonitis.

With a more extensive knowledge of pneumothorax, with a better understanding of the laws governing it, and with a sound clinical judgment as to the time of initiation of pneumothorax, fewer and fewer cases with be allowed to drift into those stages in which pneumothorax is but a doubtful indication and is at best only an ameliorative measure.

Expansile pneumothorax might even be tried in incipient cases, inasmuch as it does augment the process of healing and offers a more speedy and much more complete anatomic recovery.

Complications are rather the exception than the rule in properly selected cases treated with expansile pneumothorax.

SUMMARY

1. Statistics on the results of artifical pneumothorax, so far collected, have little value because the kind of pneumothorax used in each case was never taken into consideration, and thus altogether unequal elements were being compared, inasmuch as the various pneumothoraces act on normal and pathological lung tissue in mechanically and physiologically different ways.

2. There are three distinct types of induced pneumothorax: (1) *Expansile pneumothorax*, in which the inspiratory intrapleural pressure is always below that of the intrapulmonary one, the uninvolved portion of the lung being collapsed but not compressed, and continues to expand and contract to a limited extent with each inspiration and expiration, while the diseased portion is rendered airless and is not affected by the respiratory movements. (2) *Static pneumothorax*, or *pneumothorax of rest*, in which the intrapleural pressure equals that of the intrapulmonary one and the collapsed lung is in a state of equilibrium or rest. (3) *Compression pneumothorax*, in which the inspiratory as well as the expiratory intrapleural pressure exceeds that of the intrapulmonary one, causing an actual compression of the lung and reducing its air capacity to the minimum.

3. There exists an intimate interpendence between the pneumodynamics and hemodynamics of artificial pneumothorax, and the compensatory adequacy of the circulatory apparatus is of great importance to the success of pneumothorax. It is greater in early cases of pulmonary tuberculosis than in old chronic cases in which its reserve energy becomes exhausted by the persistent toxemia.

4. The mediastinum becomes deflected and curved toward the contralateral side only where the expiratory intrapleural pressure reaches about zero, and even the most labile mediastinum will therefore encroach very little upon the untreated lung in expansile pneumothorax, while compression pneumothorax can never be obtained in the presence of a labile mediastinum without causing the most distressing dyspnea.

5. Compression pneumothorax should rarely be applied, and only in those cases in which marked fibrosis and adhesions require a high pressure in order to become effectively compressed, and it should be looked upon as a palliative measure only. Static pneumothorax is only a transitional phase, through which any of the others must pass at some time or other. Expansile pneumothorax is the most ideal and should be used

as the treatment of choice in early cases of pulmonary tuberculosis with acute or subacute clinical course. It throws very little of the respiratory burden upon the other lung; it affects the mediastinum very slightly; it occasions lesser and more gradual changes in the pulmonary circulation; it does not give rise to complications very frequently; and it offers a more complete functional and anatomic recovery.

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OBSERVATIONS CONCERNING THE CONTRALATERAL LUNG IN PULMONARY TUBERCULOSIS TREATED BY ARTIFICIAL PNEUMOTHORAX[1]

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The indications and contraindications for collapse therapy seem to be fairly well defined, as far as the "worse diseased lung" is concerned, at least in the minds of most of the men who are practising the treatment. There is, however, a wide divergence of opinion as far as the opposite lung is concerned, particularly as to the amount and character of disease which will permit a collapse with safety and a successful issue.

Considering this great diversity of opinion regarding the indications and contraindications for artificial pneumothorax as far as the contralateral lung is concerned, we have deemed it pertinent to present our observations which have been carried on in the period, 1911 to 1923, during which time 600 cases of pulmonary tuberculosis were subjected to artificial-pneumothorax treatment.

This study has to do only with the chronic types of tuberculosis, particularly with the fibrocaseous and fibrocaseous cavernous groups, 423 cases, for the reason that they lend themselves to longer continued observations, and therefore more accurate conclusions, than the acute forms of tuberculosis and those cases in which the collapse was done only as a palliative procedure, to control severe symptoms, hemoptysis, etc.

The 423 cases in which collapse was attempted or carried out were classified into the groups given in table 1. According to the N. T. A. Classification, 358 cases were far advanced and 65 cases were moderately advanced.

TABLE 1

	CASES
Chronic fibrocaseous tuberculosis, progressive, with little or no demonstrable excavation	194
Chronic fibrocaseous cavernous tuberculosis, progressive	177
Chronic fibrocaseous cavernous tuberculosis with cavity manifestations in the foreground	52

[1] Read at the Twentieth Annual Meeting of the National Tuberculosis Association, Atlanta, Georgia, May 8, 1924.

The end-results of pneumothorax therapy are so intimately associated with and dependent upon the behavior of the contralateral lung, that, if accurate deductions based upon a comparison of end-results are to be made, it is essential that a classification of the status of the opposite lung be adopted. In this way one will be able to estimate, with a fairer degree of accuracy, the prognostic significance of the various types of contralateral lung disease before subjecting the patient to collapse therapy. While we realize that many types of pathological change may coexist in the opposite lung, those cases which we subjected to pneumothorax usually presented a dominant type which we classified as shown in table 2.

TABLE 2

	CASES
Essentially negative	97
Deep peribronchial infiltration	103
Disseminated bronchogenic caseous extensions	40
Active fibrocaseous infiltration	134
Quiescent fibrocaseous infiltration	49

DESCRIPTION OF CLASSIFICATION

1. Essentially negative: It is frequently difficult, if not impossible, to demonstrate hidden or obscure foci of infection in the contralateral lung, but in the cases which we have classified as *Essentially Negative* the physical and roentgenological findings were well within the limits of normal disparity.

2. Deep peribronchial infiltration: The physical examination is as a rule negative, aside from questionable alterations in breath-tones, with an entire absence of moisture. The diagnosis of this lesion is based largely upon roentgenological findings, and is characterized by a marked increase in the shadows of all or parts of the bronchial tree, especially of those shadows radiating from the hilum toward the superficies.

These shadows usually present an irregular, beady or varicose arborization, with fuzzy or clear-cut borders, depending upon the age and activity of the lesion.

In view of the presence of an active tuberculosis in the other lung, roentgenological findings of this character justify the diagnosis of deep peribronchial infiltrations, undoubtedly tuberculous.

The peribronchial type of tuberculous infiltration *per se*, from a standpoint of pneumothorax therapy, does not require great consideration as long as it remains confined to the peribronchial structures.

These infiltrations are not always benign in character, for in lesions of this type there is a tendency to invasion of lung parenchyma, and when this occurs it becomes a matter of serious import, especially when happening during the course of pneumothorax therapy.

Invasion of lung parenchyma is usually readily demonstrable by physical diagnostic methods and its evolution may be watched by the study of serial plates.

3. Disseminated bronchogenic caseous extensions: These lesions, so constant in the study of gross pathological changes, usually occur as a result of the aspiration of bacilli-laden sputum into the contralateral lung, and are characterized by the presence of localized caseous pneumonic, caseous bronchopneumonic and disseminated confluent tuberculous infiltrations, frequently associated with a tuberculous bronchitis. These bronchogenic extensions usually take place into the dependent portions of the lung or into the perihilar region. Roentgenologically, they are revealed as disseminated patches of increased density, corresponding to the distribution of the lesions and varying in character according to the activity or inactivity of the process. If deep-seated, they may escape physical diagnostic procedures, but if superficial they are readily recognized by the continual presence of moisture and alterations in breath-tones.

4 and 5. Active and quiescent fibrocaseous infiltrations: These lesions, in contradistinction to the bronchogenic infections above described, usually occupy the upper half of the lung. They are readily recognized by the usual physical diagnostic and roentgenological procedures, although there is a frequent disproportion between physical and roentgenological findings, and to place sole reliance upon one or the other alone will frequently lead one astray. The activity or inactivity of the process is determined by a correlation of these findings. As a rule, the presence of moisture indicates activity, although its absence by no means indicates quiescence.

Moisture, when present, must be carefully studied in order to determine its pathological significance. An effort should be made to elicit and to differentiate those râles characteristic of fresh invasion or destructive lesions, from those associated with an obsolete or retrogressive process. Râles which occur in the form of fine showers on deep inspira-

tion or on expiratory cough almost invariably indicate fresh invasion. Destructive lesions are usually associated with abundant râles which are more or less numerous, according to the rapidity of the process. They possess a resonating or metallic quality and they vary in character according to the character of the excavation from which they arise. Retrogressive or stationary lesions are more often associated with râles of a nonresonating character, are less numerous and are best elicited on the first inspiration following expiratory cough.

Retrogressive and healed lesions are accompanied by fibrosis which causes dilatation of terminal bronchioles. Even excavated areas may heal and become lined with a mucosa; thus, the tuberculous process, as such, really no longer exists.

These changes may be associated with abundant râles which are more or less persistent, but one should be familiar with their pathological significance and not be confused by their presence, as they are evidences of an obsolete or healed lesion. When these changes are encountered over a small localized area, collapse of the opposite lung is not always contraindicated.

Râles arising as a result of adhesive pleuritis and atelectasis can be readily confused with râles of great significance. Râles associated with an adhesive pleuritis occur as superficial crackles, best heard on forced respiratory movement, and they do not appear in the form of showers on expiratory cough. Atelectatic crackles are usually heard along the margin of the lung. These crackles disappear after a few inspirations and are never persistently present in the same location day after day.

The fibrocaseous lesions present fairly characteristic roentgenological markings. The roentgenograph will supply evidence tending to prove the age of the lesion and, in a measure, also the activity or inactivity of the process. Early infiltrative lesions may escape roentgenological recognition, and are at times best recognized stethoscopically.

The more active and progressive lesions are characterized by patch-like spots with indefinite irregular borders, whereas the quiescent and retrogressive processes are represented by more linear markings with more sharply circumscribed borders.

As a rule, auscultation will elicit exaggeration in breath-tones, both in the active and quiescent lesions. One must carefully differentiate, however, that type of exaggerated breathing heard over fresh invasion from the compensatory type of breathing so frequently heard in the contralateral lung.

SELECTION OF MATERIAL AND CONTROL OF TREATMENT

The recognition, interpretation and classification of these various lesions in the opposite lung are of paramount importance in the selection of material, and great caution should prevail in their treatment.

Early in our work we were loath to subject to pneumothorax therapy any case presenting more than minimal traces of disease in the contralateral lung, except as a last resort.

As a result of the observations made during the treatment of some of these last-resort cases, we realized that not infrequently excellent results, occasionally leading to complete recovery, could be obtained, even in the presence of extensive disease in the opposite lung. The results, however, were dependent upon many factors, such as the character of collapse, flexibility of mediastinum, type of opposite lung lesion, and vigilance exercised as to changes taking place therein.

We have observed that a diseased lung varies greatly in its reaction to collapse of the other side; and we have learned that certain types of contralateral lung disease can be approached with relative safety, while other types are approached with great reluctance and apprehension.

As a general rule the fibrocaseous lesions involving the apex or upper portion of the lung react much more favorably than the fibrocaseous lesions located around the root of the lung, or the bronchogenic caseous extensions scattered throughout the lower portions of the lung.

This difference in reaction may be due to the fact that upper-lobe lesions are more firmly immobilized by fibrosis and pleuritic thickening, and are usually favored with better drainage, while lower-lobe lesions are unfavorably influenced by being subjected to greater amplitude of respiratory motion, which inhibits fixation and favors aspiration and dissemination, which are further enhanced by poorer drainage.

Furthermore, certain types of lesions, especially those in the perihilar region, are kept in constant motion by cardiac activity, which the fluoroscope will readily reveal as a constant tugging and pulling that are synchronous with each heart-beat.

All patients reported in this series received sanatorium treatment, many of them having been under observation for long periods of time, and had exhausted various climatic, dietetic, and hygienic procedures. The delay in treatment in many cases was very unfortunate, because when we were obliged to resort to an artificial pneumothorax, we were unable to introduce gas on account of the presence of adhesions. Of

recent years we have felt that, if after a brief period of observation, one to three months, any doubt exists as to the favorable outcome by the usual sanatorium regimen, collapse therapy should be immediately instituted if no contraindications exist. This is particularly imperative in cavity cases with abundant expectoration, in which there exists constant danger of infection, not only of the opposite lung by aspiration, but of the bowel through deglutition, and of the larynx through lodgment of sputum.

Any procedure which has for its object the reduction of sputum quantity, thus lessening the danger of these complications, is justifiable; and we have felt that our tardiness in utilizing pneumothorax treatment was responsible for many failures, through the development of these various complications.

Notwithstanding the danger of delay, if the contralateral lung lesion is very active, it is better to allow the activity of the process to subside somewhat before resorting to collapse, but this furthermore enhances the danger of the formation of adhesions. If the disease in the contralateral lung is not too active, this danger can be minimized by interposing a thin layer of gas, thus separating the worse diseased lung from the chest-wall to the extent of an inch or two, and then maintaining this character of collapse while observing the behavior of the opposite lung. Frequently we have noted the beneficial effects of these small degrees of collapse, not only in the worse diseased lung, but also in the contralateral lung, particularly in the fibrocaseous lesions involving the upper portion. By this manner of approach we have, in many cases, been enabled to bring about a gradual satisfactory collapse of the worse diseased lung with an uninterrupted improvement of the opposite lung process, even leading to complete recovery. In some cases, collapse has been carried out for years without any appreciable influence on the opposite lung process. In other cases, in spite of our watchfulness and care, progression of disease took place in the opposite lung. In still other cases the contralateral lung lesion remained stationary for years, later on becoming rapidly progressive and demanding a pneumothorax.

During the period of sanatorium treatment all patients were taught a method of chart-keeping, whereby the temperature and pulse were recorded in a graphic manner, and the charts were continued during the whole course of their pneumothorax treatment. They were also made acquainted with the extent and character of their disease, results of all examinations and the principles of pneumothorax treatment, thus

enabling them to render more intelligent coöperation. All or most cases were discharged to ambulant care at the earliest possible moment compatible with safety.

Having established the indications for collapse therapy as far as the worse diseased lung is concerned, there still remains the important task of estimating the integrity of the opposite lung, for, after instituting a pneumothorax, one will frequently be confronted with the problem of having to decide whether or not unfavorable symptoms are emanating therefrom.

A solution of this problem will be greatly facilitated by always maintaining accurate records of the status of the contralateral lung. These records should contain the exact topographical distribution of physical findings recorded before each inflation, and as often as necessary during the interval. Râles, if present, should be studied and the following points carefully noted: Whether they appear only on expiratory cough or on first inspiration following, or whether they are present on ordinary breathing. Their character, amount and exact anatomic distribution should be recorded, so that the record can be compared with all previous examinations.

The roentgenological control must be carried out with great frequency. It is our custom to make a fluoroscopic examination from which an orthodiagram is prepared, before each inflation, and during the early phases of the collapse it is imperative to resort to the fluoroscope more frequently, in order to determine better the proper interval for inflation.

Each individual patient is a law to himself as far as reaction of the lung to inflation and absorbability of gas are concerned, and difficulties will be encountered sooner or later if a fixed plan is adopted as to the time interval and as to the amount of gas introduced. By the frequent recourse to the fluoroscope, one will be better able to adapt oneself to these varying factors which each patient may present.

Unless the use of the fluoroscope is resorted to freely, the integrity of the contralateral lung may be threatened after the first few inflations through undue stress placed upon it by great displacement of mediastinal contents, which might otherwise easily escape detection. One should not depend solely upon manometric pressure readings and physical findings to determine the character of collapse.

In the roentgenological control of the contralateral lung the fluoroscope alone is inadequate, and one must depend upon frequent use of films for

the reason that early fresh invasions escape fluoroscopic detection, even if roentgenologically present.

Too much reliance should not be placed upon the examination of a single film in any case, presenting actual or threatened invasion of the opposite lung; but the last film should be minutely compared with the previous films, for it is possible only in this manner to evaluate the exact changes taking place. In the interpretation of the markings in the contralateral lung, one must differentiate between actual pathological changes and changes due to circulatory stasis, which are especially marked in cases presenting a bulging mediastinum.

In doubtful cases the differentiation is facilitated by permitting a slight reëxpansion of the collapsed lung, thus allowing the mediastinum to assume a more normal position, when the shadows due to circulatory disturbance rapidly disappear.

Disease in the contralateral lung is best revealed on films taken at the height of deep inspiration, but changes in the position of the mediastinum are best seen in films taken at the end of expiration. By comparison of the films taken in these two positions it is interesting to note the great excursion which can taken place in a labile mediastinum.

X-ray films have the distinct advantage of supplying a permanent record.

During the early phases of collapse therapy, films should be made after every third or fifth inflation if one resorts to small amounts of gas at short intervals, and later on, after the first two or three months, films should be made at monthly intervals. Ambulant cases are "filmed" at least once every three months throughout the whole course of their treatment.

In the selection of material, and in the control of treatment, one always has to contend with the transmission of auscultatory findings from the worse diseased lung to the opposite side. From a physical diagnostic standpoint alone, it will be exceedingly difficult to differentiate these transmitted auscultatory phenomena from those due to actual disease, but an endeavor should be made to find out their source, by localizing their point of maximum intensity and, in the case of transmitted phenomena, one will be led to the opposite lung. A decision will be further facilitated by a study of X-ray films, which will reveal an entire absence of disease in the contralateral lung that could account for the character of the auscultatory findings. The flexibility of the mediastinum will also have an important bearing on adventitious sounds elicited

in the contralateral lung, for occasionally râles, when present in the opposite lung before inflation, will change in character, or disappear immediately afterward, in the presence of a flexible mediastinum.

ANALYSIS OF CLINICAL PHENOMENA

In the presence of actual or threatened invasion of the opposite lung, one is continually confronted with the task of having to exclude the contralateral lung as a source of any unfavorable clinical signs or symptoms, the most serious of which are the following: fever, increased expectoration and hemoptysis.

Febrile reaction following inflation, or the regular occurrence of an ephemeral exacerbation of temperature within twenty-four hours after inflation in the presence of a satisfactory collapse, should lead one to suspect the opposite lung, particularly in the absence of an exudate or of adhesions.

Recurrence of fever following an afebrile period occurs most commonly under the following conditions: appearance of exudate in pneumothorax cavity, insufficient collapse, that is, reëxpansion of lung, progression or extension of disease in contralateral lung, extrapulmonary tuberculous complications, especially enteritis, and acute nontuberculous respiratory infections.

Fluoroscopy alone will suffice to reveal an exudate and aspiration will usually cause subsidence of fever.

Difficulty will at times arise in differentiating fever, due to progression or extension of disease in the contralateral lung, from fever due to insufficient collapse, that is, reëxpansion of lung.

A solution of this question is exceedingly important, for to be misled at this juncture might convert a possible successful end-result into a failure. If the fever is due to reëxpansion, a delay in inflation will permit further progression of disease in the collapsed lung, and it also involves the danger of an early obliterative pneumothorax. If the fever is due to progression or extension of disease in the contralateral lung, further compression would only aggravate this disease already present. In arriving at a decision, the contralateral lung must be subjected to a searching examination, the results of which must be minutely compared with the records of previous examinations (films and physical). If, after this comparison, there is no evidence of fresh invasion or progression of disease in the opposite lung, then further collapse is justifiable.

Fever due to extrapulmonary tuberculous complications is usually

associated with localizing symptoms, which develop coincidently with or shortly after the febrile reaction, and is uninfluenced by inflation. Fever of this character may be due to an obscure tuberculous enteritis, from which the patient complains of no subjective symptoms or only of mild gastrointestinal disorder. The cause of the fever may escape detection unless especially sought for, particularly in the presence of contralateral lung disease which is always to be suspected. As a rule, contralateral lung disease will be excluded as an etiological factor in the production of the fever, as here again the inflations will have no relationship to the remissions and exacerbations of the irregular type of fever which is present in tuberculous enteritis. An ischiorectal abscess, acute or chronic, can at times account for this type of fever.

Fever due to acute infections may be confusing during the period of its onset; and, until the localizing symptoms appear, one will be led to suspect the contralateral lung, especially if it is already diseased. The most common of these are the acute infections of the upper respiratory tract, tonsils, sinuses and teeth.

Fever which is continuous in spite of apparently satisfactory collapse, such as minor degrees of continuous fever, 99 to 99.6°, is occasionally encountered in patients who are otherwise apparently clinically well. This type of fever is at times very annoying to the patient, as well as to the physician, and for a time the cause escapes detection. It must be borne in mind that this type of fever is not always due to the tuberculous process itself, but it may be due to nontuberculous complications, such as chronic focal infections, thyrotoxicosis, etc., which not uncommonly coexist in the tuberculous patient.

There is, however, this distinction: that when the fever is due to tuberculosis it is more responsive to rest and more aggravated by exercise, whereas the fever due to a nontuberculous process is not influenced to such an extent. When fever of this type is due to contralateral lung disease, it is usually associated with other evidence of a clinical, physical diagnostic or roentgenological nature, which will be revealed after sufficient observation.

Another type of continuous fever encountered is that in which treatment has been associated with a reduction of fever amounting to two or more degrees, but there still remains an average daily maximum of 100.6° in spite of a satisfactory collapse. When temperature of this character is due solely to contralateral lung disease, auscultation alone will usually supply ample evidence of its origin.

INFLUENCE OF CONTRALATERAL LUNG DISEASE ON SPUTUM

Of equal importance in eliminating the contralateral lung as a factor in the causation of fever is its elimination as a source of bacilli-laden sputum, in the presence of a collapse of the worse diseased lung.

The persistence of bacilli-laden sputum, with an essentially negative contralateral lung and in the presence of an *apparently* satisfactory collapse, indicates that diseased tissue is not sufficiently collapsed, either because of the presence of adhesions, particularly apical, which are not always revealed by X-ray films, or because of the presence of rigid-wall excavations. However, the persistence of bacilli-laden sputum in quantities of 20 or 25 cc. daily, in the presence of a diseased contralateral lung and with an *apparently* satisfactory collapse of the worse diseased side, should lead one to strongly suspect the contralateral lung as a source, particularly when auscultation reveals moisture in it.

Under these circumstances one will be obliged to decide whether to allow of moderate reëxpansion, thus relieving the contralateral lung, or to further collapse the worse diseased lung. When confronted with this problem, it is essential that the twenty-four-hour quantity of sputum should be measured carefully each day, and its relationship to inflation and physical findings in each lung closely observed.

The influence of inflations on the temperature curve should be observed as well, for, in the presence of contralateral lung disease, inflations are sometimes followed by an exacerbation of temperature, which, when associated with an increase in sputum amount, points more strongly to the contralateral lung as a source.

If the contralateral lung is responsible for the increased expectoration, the physical examination will usually reveal an increase in the amount of râles, as well as an increase in their distribution, when compared with previous examinations.

Stereoscopic films should be made, and these should be carefully compared with all previous films, and if the contralateral lung is to blame for the sputum increase corroborative evidence will usually be manifest as a progression of disease.

The influence of the patient's bed posture during coughing paroxysms and lung drainage should be carefully observed, as much valuable evidence may be supplied that may tend to show the side from which the sputum emanates, as some positions will be associated with freedom from cough and expectoration, due to retention of secretion in dependent por-

tions of the lung, whereas other positions will provoke coughing paroxysms with abundant expectoration due to free drainage.

A final decision can best be reached only after a correlation of all findings.

HEMOPTYSIS

Severe hemoptysis occurs at times in the course of pneumothorax treatment, and always directs attention to the contralateral lung, particularly if it is diseased. In a series of 480 collapsed cases (all types of tuberculosis) severe hemoptysis was present preceding or shortly before pneumothorax treatment was begun in 82 cases, but after pneumothorax treatment was instituted hemoptysis occurred in only 10 cases.

It is notoriously difficult to determine from which side bleeding is having its source, particularly when one is dealing with a diseased contralateral lung, but the accurate determination of this point is imperative, for if the bleeding is proceeding from the collapsed lung, further collapse is demanded; while if from the opposite lung, further collapse is strongly contraindicated. The determination of the bleeding side is complicated by reason of the hesitancy in submitting the patient to a searching physical examination in the presence of active bleeding. Much valuable information will be obtained from the patient's own statement regarding certain subjective phenomena which he has experienced immediately before or very early during the hemoptysis. These sensations are commonly described as a sense of tightness, constriction, pain, "rattling," or "fluttering," the exact location of which the patient will indicate with absolute confidence and assurance. These statements may be misleading, but they are, nevertheless, deserving of consideration.

As a result of bleeding, aspiration of blood occurs into dependent portions of the lung, and it is always more extensive on the bleeding side. The presence of this blood will furnish auscultatory evidence in the form of râles which are quite characteristic, and may be readily heard in portions of the lung into which aspiration has taken place. These râles have been variously described as "medium" or "small bubbling," or "crackles." At first they are nonresonating and only become resonating later on, with the development of consolidation.

COMPARATIVE SIGNIFICANCE OF THE VARIOUS TYPES OF CONTRALATERAL LUNG LESIONS BASED UPON END-RESULTS

A valuable aid in the selection of material and in determining the indications for collapse will be furnished by a comparison of end-results in the various types of contralateral lung lesions, whereby one will be able to judge the prognostic significance of disease in the contralateral lung, with collapse of the worse diseased side.

TABLE 3

End-results in 423 cases of fibrocaseous and fibrocaseous cavernous tuberculosis

STATUS OF CONTRALATERAL LUNG	NUMBER OF CASES	CHARACTER OF COLLAPSE	NUMBER OF CASES	CLINICALLY WELL		ARRESTED		DEAD	
				Number	Per cent	Number	Per cent	Number	Per cent
Essentially negative	97	Satisfactory	56	29	52	11	20	8	14
		Partial	25	10	40	1	4	6	24
		No free space	16	4	25	1	6	9	56
Deep peribronchial infiltration	103	Satisfactory	49	24	45	12	24	10	20
		Partial	33	3	9	7	21	20	60
		No free space	21	1	4	3	13	9	43
Disseminated bronchogenic caseous extension	40	Satisfactory	15	4	26	4	26	5	33
		Partial	21	1	4	5	24	14	66
		No free space	4	0	0	0	0	3	75
Active fibrocaseous infiltration	134	Satisfactory	50	24	48	11	22	11	22
		Partial	59	4	6	12	20	27	46
		No free space	25	0	0	3	12	19	76
Quiescent fibrocaseous infiltration	49	Satisfactory	21	10	50	5	24	4	20
		Partial	16	4	25	6	37	6	37
		No free space	12	2	16	2	16	4	33
	423		423	120		78		155	

A study of the table of end-results (table 3), with a view of determining the significance of the contralateral lung lesions, will reveal that of the 423 cases subjected to artificial-pneumothorax treatment, 326 cases had demonstrable disease in the opposite lung, and in 223 of these it amounted to well-defined fibrocaseous infiltrations or disseminated bronchogenic extensions. It will be seen that only 23 per cent of the cases included in this series presented an essentially negative contralateral lung.

The "No Free Pleural Space" cases have been included in this series for the reason that they serve as invaluable controls; for, aside from the fact that they received no pneumothorax treatment, their treatment was identically the same in every other respect.

The inclusion of the "No Free Pleural Space" cases is also important because a study of table 3 will reveal that satisfatory end-results are as much dependent upon the presence of free pleural space and the character of collapse attained as they are upon the presence or absence of disease in the opposite lung.

Of the 423 cases, 97 had an "Essentially Negative" opposite lung. Of this number, 56 secured a satisfactory collapse, of which 52 per cent are clinically well, 20 per cent are arrested and 14 per cent are dead.

Of the 423 cases, 103 had a deep peribronchial infiltration in the opposite lung. Of this number, 49 received a satisfactory collapse, of which 45 per cent are clinically well, 24 per cent are arrested and 20 per cent are dead.

It will be noted in comparing the deep peribronchial infiltration with the essentially negative contralateral lung, that in the presence of a satisfactory collapse there are 7 per cent less clinically well and 6 per cent more dead in the former than there are in the latter group.

Of the 423 cases, 40 cases had disseminated bronchogenic caseous extensions in the opposite lung. Of this number, 15 received a satisfactory collapse, of which 26 per cent are clinically well, 26 per cent are arrested and 33 per cent are dead.

Thus, from a prognostic standpoint, this type of contralateral lung lesion is of serious import; for, when compared with the essentially negative contralateral lung group, it will be seen that there are 26 per cent less clinically well and 19 per cent more dead in the former than in the latter group.

Of the 423 cases, 134 had an active fibrocaseous infiltration in the opposite lung. Of this number, 50 received a satisfactory collapse, of which 48 per cent are clinically well, 22 per cent are arrested and 22 per cent are dead.

In comparing this type of contralateral lung with the essentially negative opposite lung, it will be observed that there are only 4 per cent fewer cases clinically well, but there are 8 per cent more dead.

Of the 423 cases, 49 had a quiescent fibrocaseous infiltration in the opposite lung. Of this number, 21 received a satisfactory collapse, of which 50 per cent are clinically well, 24 per cent are arrested and 20 per cent are dead.

In comparing the active with the quiescent fibrocaseous infiltrations, it will be seen that there are 2 per cent more clinically well, 2 per cent more arrested and 2 per cent less dead in the quiescent than in the active fibrocaseous groups.

This difference in end-results is not as great as one would expect in a comparison of an active with a quiescent fibrocaseous opposite lung, but it is probable that activity undoubtedly existed in some cases which we were obliged to classify as quiescent because of our inability to demonstrate activity, even though it was suspected. However, these figures are entirely consistent when one compares the end-results (table 4) in both the active and quiescent fibrocaseous opposite lung lesions, with the essentially negative contralateral lung.

TABLE 4

Comparison of end-results in active and quiescent fibrocaseous contralateral lung with essentially negative contralateral lung in presence of a satisfactory collapse

STATUS OF CONTRALATERAL LUNG	CLINICALLY WELL	ARRESTED	DEAD
	per cent	*per cent*	*per cent*
Essentially negative	52	20	14
Quiescent fibrocaseous infiltration	50	24	20
Active fibrocaseous infiltration	48	22	22

As previously stated, the disseminated bronchogenic caseous extensions, occupying the perihilar and lower portions of the lung, offer a much more unfavorable outlook than the fibrocaseous lesions usually occupying the upper portions of the lung.

A study of end-results in the following table (table 5) will reveal that the disseminated bronchogenic caseous extensions are the most serious type of contralateral lung lesions with which we have had to deal.

TABLE 5

Comparison of end-results: essentially negative with certain types of contralateral lung disease in the presence of a satisfactory collapse

STATUS OF CONTRALATERAL LUNG	CLINICALLY WELL	DEAD
	per cent	*per cent*
Essentially negative	52	14
Active fibrocaseous infiltration	48	22
Quiescent fibrocaseous infiltration	50	20
Disseminated bronchogenic caseous extensions	26	33

From a study of the above statistics, as regards the percentage clinically well and dead in the presence of a satisfactory collapse, it might be held by some that results equally satisfactory are attained by the usual sanatorium regimen without pneumothorax.

However, the value of pneumothorax therapy in this series will be clearly shown by a comparison of the end-results in cases satisfactorily collapsed (table 5) with those having "No Free Pleural Space," which serve as controls (table 6).

TABLE 6

End-results in noncollapsed cases (no free pleural space)

STATUS OF CONTRALATERAL LUNG	CLINICALLY WELL	DEAD
	per cent	*per cent*
Essentially negative	25	56
Active fibrocaseous infiltrations	0	76
Quiescent fibrocaseous infiltrations	16	33
Disseminated bronchogenic caseous extensions	0	75

It will be observed that in this series, from a study of table 3, a patient's opportunity for recovery was much better with any type of contralateral lung disease in the presence of a satisfactory collapse than in the case of the patient who had an essentially negative lung, in which collapse was not possible on account of our inability to find a free pleural space.

OBSERVATIONS ON PROGRESSION AND EXTENSION OF DISEASE IN CONTRALATERAL LUNG

The term "Progression of Disease" refers to those cases in which there was exacerbation of disease in a contralateral lung already diseased, whereas the term "Extension of Disease" refers to those in which invasion of an essentially negative contralateral lung took place.

In compiling our statistics we have included in our figures only those instances of progression or extension of disease in the contralateral lung, in which these complications occurred during the actual period of pneumothorax treatment.

Undoubtedly progression and extension of disease took place in the terminal phases of many cases after pneumothorax treatment was abandoned, particularly in the progressively fatal cases, but they were not included for the reason that the development of these complications was not associated with or related to the period of collapse therapy.

No doubt, minor degrees of progression and extension of disease took place in some cases, but it was of a character which escaped physical diagnostic or roentgenological methods of recognition.

It is also true that many cases experienced alternating periods of exacerbation and quiescence of activity of contralateral lung disease while under collapse, but the periods of exacerbation were temporary and were not of a character demanding discontinuance of collapse therapy.

Whether these exacerbations occurred in spite of, or were dependent upon collapse, is impossible to say, because changes of this nature are not infrequent throughout the course of any tuberculous process.

When progression of disease in the opposite lung is of a mild nature, a prolongation of intervals and the introduction of small amounts of gas are necessary, thus permitting of some reëxpansion of the collapsed lung, which will frequently bring about a subsidence of the activity in the contralateral lung and a coincident improvement.

Severe and rapid progression of disease in the contralateral lung demands temporary cessation of pneumothorax treatment. Under circumstances of this nature, one will be confronted with a complicated problem to decide upon future procedure. A decision will be reached after a brief period of observation, and one will be guided in this decision by the behavior of both lungs during this period.

When reëxpansion of the collapsed lung is not followed by reactivation of disease therein, one will be justified in considering the feasibility of bilateral collapse. Should this procedure be adopted, the primarily collapsed lung should be permitted to reëxpand as much as possible without evidence of reactivation of disease in it, and at the same time it must still be under control, so that recollapse can be instituted as indications require. If no reactivation occurs, one can then proceed cautiously with the contralateral lung collapse. The inflations should then be made alternately, the intervals and amounts of gas being determined by the indications and contraindications in each lung. We have carried out bilateral collapse in 14 cases, 2 of which are clinically well and 12 are dead. The prognosis in cases so severe as to demand a bilateral pneumothorax is very grave, but the procedure will often add much comfort and prolongation of life to the patient.

Out of the 423 cases included in this study, 345 cases were collapsed. Of the 345 collapsed cases, 264 had demonstrable disease in the opposite lung, 82 cases having well-defined deep peribronchial infiltration, *but in 182 cases the disease amounted to fibrocaseous infiltrations or dis-*

seminated bronchogenic caseous extensions. In these 264 cases progression of disease in the contralateral lung took place in 24 cases as shown in table 7.

TABLE 7

Progression of disease in the contralateral lung in collapsed cases

STATUS OF CONTRALATERAL LUNG	NUMBER OF CASES	PROGRESSION NUMBER CASES	CHARACTER OF COLLAPSE
Deep peribronchial infiltrations	82	2	2 partial
Disseminated bronchogenic caseous extensions	36	3	1 satisfactory 2 partial
Active fibrocaseous infiltrations	109	17	7 satisfactory 10 partial
Quiescent fibrocaseous infiltrations	37	2	2 partial

INFLUENCE OF PARTIAL COLLAPSE ON CONTRALATERAL LUNG

Conclusions drawn from a statistical analysis of the behavior of the contralateral lung in the presence of a partial collapse of the worse diseased side are unreliable for the reason that the more the partial collapse partakes of the character of a satisfactory collapse, the more the end-results will approach those of a satisfactory one and, contrariwise, the more limited or localized the partial collapse, the more the end-results will approach those of the "No Free Space" cases. Furthermore, the end-results in pneumothorax therapy in cases under partial collapse are, for the most part, so little influenced by the behavior of the contralateral lung and so dependent upon the type of disease in the worse diseased lung and the character of collapse, that any deductions based upon the various types of contralateral lung disease would certainly lead to erroneous conclusions.

There can be no constant uniformity in end-results in cases under partial collapse, for the reason that there is no uniformity in the character of partial collapse. It would be misleading to compare the end-results of a case with an active fibrocaseous contralateral lung with a partial collapse which approached a satisfactory collapse, with a case with an essentially negative contralateral lung in which the pneumothorax was very limited or transitory in character.

Even with these facts in mind, reference to table 3 will reveal certain illogical discrepancies in the partial-pneumothorax group which might lead to erroneous conclusions unless one was familiar with the circumstances surrounding these cases.

For example, in the "Deep Peribronchial Infiltration" group under partial collapse, there were 33 cases, 60 per cent of which are dead, whereas of 21 "No Free Pleural Space" cases, with the same type of contralateral lung, only 43 per cent are dead, which would lend support to the opinion that in the "Deep Peribronchial" cases the partial pneumothorax was not only of no value but was actually detrimental. An examination of the individual case-records of this group shows that the partial collapse was of value, for 16 were temporarily improved and only 4 were progressively fatal, whereas all the "No Free Pleural Space" control cases were progressively fatal.

Furthermore, even though these 16 improved cases were ultimately fatal, they should not be altogether chargeable to partial-pneumothorax failures, since 3 cases died of intercurrent disease not related to tuberculosis. Three more patients in this group who voluntarily discontinued treatment, believing themselves cured, later suffered a relapse of their disease which proved fatal. Three additional cases, which were steadily improving under sanatorium regimen, left the sanatorium against advice and lived under very unfavorable social and economic conditions, which undoubtedly provoked a reactivation of disease.

As further evidence of the favorable influence of a partial pneumothorax in this group of cases, 32 out of 33 cases under partial compression had a tubercle-bacillus-positive smear before pneumothorax treatment and only 14 had a positive smear on discontinuation of pneumothorax treatment, whereas of the 20 "No Free Pleural Space" cases, 19 had a positive smear before sanatorium treatment and 14 had a positive smear upon discontinuation of treatment.

Out of 81 cases with an essentially negative contralateral lung, extension was noted in 4 instances, 3 of which were satisfactory collapses and the extension was of such a character that it required discontinuation of pneumothorax treatment.

Pleurisy with effusion in the contralateral lung occurred in 5 cases, four of which had an active fibrocaseous infiltration in the contralateral lung and one had a disseminated bronchogenic caseous extension into the contralateral lung.

CONCLUSIONS

1. A classification of the status of the contralateral lung is necessary if accurate deductions based upon end-results are to be made.

2. The end-results of pneumothorax therapy are less dependent upon the status of the contralateral lung than they are upon the character of collapse and type of disease in the worse diseased lung.

3. The various types of contralateral lung lesions vary greatly in their prognostic significance.

4. Fibrocaseous infiltrations involving the upper portion of the lung offer a more favorable prognosis than the bronchogenic extensions into the lower portions of the lung.

5. The mere presence of disease in the contralateral lung does not contraindicate collapse of the worse diseased side.

6. Râles in contralateral lung disease must be carefully studied in order to determine their pathological significance.

7. The absence of râles in a diseased contralateral lung by no means indicates absence of activity.

8. Cavity cases with abundant expectoration should be subjected to early pneumothorax treatment in order to prevent aspiration infection of the opposite lung.

9. Very active contralateral lung disease should be allowed to subside before instituting pneumothorax on the worse diseased side.

10. In the presence of contralateral lung disease great caution should prevail in collapse of the worse diseased lung.

11. In some cases, the worse diseased lung should be held merely separated from the chest wall pending observation of the behavior of the contralateral lung.

12. Flexibility or rigidity of the mediastinum plays an important rôle in the behavior of the contralateral lung during collapse.

13. Excellent results are occasionally attained by cautious collapse, even in the presence of extensive contralateral disease.

14. Satisfactory end-results are frequently proportionate to the degree of watchfulness accorded the contralateral lung.

15. The status of the contralateral lung should be observed by frequent physical and roentgenological examination, and accurate records should always be maintained.

16. Auscultatory phenomena transmitted from the worse diseased to the contralateral lung should be differentiated from those findings due to active disease in the contralateral lung.

17. The contralateral lung, when diseased, should always be suspected when unfavorable clinical symptoms arise.

18. In this series, in the presence of a satisfactory collapse of the worse diseased lung, end-results were much better with any type of contralateral lung lesion than those of the "No Free Pleural Space" cases, with an essentially negative contralateral lung.

19. Out of 345 collapsed cases, progression of disease in the contralateral lung, demanding discontinuance of pneumothorax treatment, took place in 24 cases.

20. Heretofore, possibly too much conservatism has been exercised in the selection of material presenting contralateral lung disease.

CONTRALATERAL EXUDATIVE PLEURITIS COMPLICATING ARTIFICIAL PNEUMOTHORAX

A Report of Three Cases

ANDREW PETERS[1]

Since the fairly general use of artificial pneumothorax as a therapeutic measure in pulmonary tuberculosis, the frequency of complicating pleural exudates on the treated side has been widely known and generally recognized. Their recognition is made easy by the presence of the accompanying pneumothorax, and if the patients are carefully followed and observed these exudates, even when slight, are not likely to be missed. Reasons have been given elsewhere (1) for considering most of these exudates of tuberculous origin. Infection of the pleura may result from fresh implantation of tubercle on the surface of the visceral pleura, from denudation of an underlying focus by tension on attached adhesions, or from progressive ulceration or advance of such a focus toward the surface. It is also, of course, possible that the mere exposure of a raw surface by the stripping of an adhesion might give rise to a sterile or traumatic inflammatory exudate into the pleura, without the exposed surface necessarily harboring a tuberculous focus, but the usual demonstration of tubercle bacilli in the exudate after animal inoculation, less commonly on direct smear, indicates that truly sterile exudates must be uncommon.

In contrast to this frequency of homolateral exudates is the comparative rarity of contralateral exudative pleurisies. Until quite recent years they appear to have been quite unknown, even to experienced pneumothorax workers. Matson (2) referred briefly to three cases in 1917, but these seem to have escaped general notice, probably because they were not reported in detail but were merely referred to in a general article in a State medical journal. All the rest of the cases, so far as we can find, have been recorded in the few years from 1920 on. They total 18, exclusive of those herein reported, and are as follows:

1920	Als, E.	1 case	(Ztschr. f. Tuberk., February, 1920)
	Fishberg, M.	1 case	(Amer. Rev. Tuberc., November, 1920)
	Sussdorf, E.	1 case	(Beitr. z. Klin. d. Tuberk., November, 1920)

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1921	de Reynier, L., and Rossel, G.	2 cases (Rev. med. d. l. Suisse Rom., March, 1921).
	Zemmin, H.	1 case (Beitr. z. Klin. d. Tuberk., April, 1921)
	Stivelman, B. P.	1 case (Am. J. M. Sc., August, 1921)
1922	Spengler, C.	5 cases (Beitr. z. Klin. d. Tuberk., March 15, 1922)
	Peters, L. S.	2 cases (J. Am. M. Ass., November 4, 1922)
1923	Lindig, W.	1 case (Beitr. z. Klin. d. Tuberk., February 17, 1923)
1924	Pisoni, E.	3 cases (Osped. Maggiore, 1924, xii, 10)

Why other instances were not noted in earlier years may be difficult to understand, since pneumothorax therapy has been employed for two or three decades. Prior to the last ten or twelve years, however, its use was not widespread, and its fairly general use in large institutions may be said to be even more recent. With the attention of the early pneumothorax workers occupied with many problems, and without the aid of the X-ray, it is possible that such a rare complication may have escaped them. That contralateral pleurisies with effusion should be unusual, if not rare, in the course of pneumothorax treatment, might be expected because, first, the contralateral lung is generally but slightly invaded by the tuberculous process, which, according to the most generally accepted criteria, should not be active in that lung; moreover, if the pneumothorax is unsuccessful in accomplishing beneficial results, or if indications of activity appear on the other side it is generally soon abandoned. We are unable, therefore, to acquiesce in the assumption that pneumothorax exerts any "specific" protective effect against a contralateral pleurisy. Even in the course of unselected cases of manifest pulmonary tuberculosis as seen at institutions, serous pleurisies are not particularly frequent (the Loomis Sanatorium records give an incidence of about 5 per cent), although if every case could be followed from its inception to its termination doubtless the incidence would be materially higher.

At the Loomis Sanatorium contralateral serous or exudative pleurisy has been recorded in three instances, all of which have come under our observation, among 229 patients receiving pneumothorax treatment at this institution (operative failures are not considered), or 1.31 per cent. Our observations follow:

Case 4286: Housewife, age 44. Admitted June 22, 1921. History of hemoptysis five months before, followed by fever; later, severe pains in left chest, night-sweats, paroxysms of coughing. A "specialist" gave her tuberculin and autogenous vaccines. Dyspnea developed, and in May, 1921, another hemoptysis and bacillary sputum. Signs of extensive involvement of left lung, with upper-lobe cavitation and infiltration about right root. Roentgenograms (see fig. 1) showed dense infiltration and consolidation on the left, with multiple cavities in

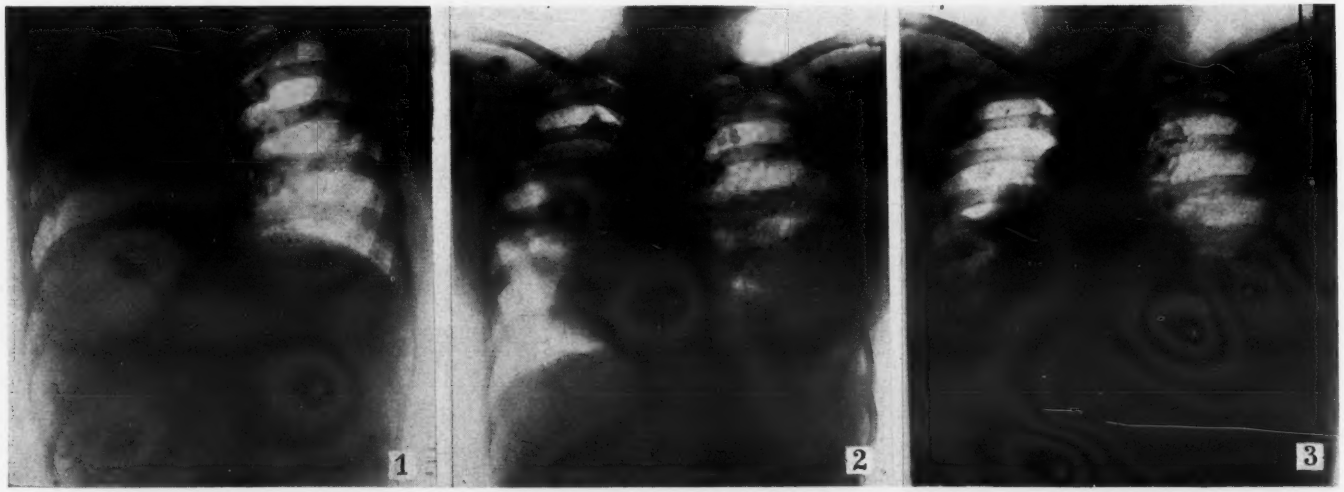

FIG. 1. CASE NO. 4286. CHEST (POSTERIOR-ANTERIOR) JULY 5, 1921

Note massive involvement of left lung, with multiple cavitation in upper lobe

FIG. 2. SAME CASE, SEPTEMBER 2, 1921

Note incomplete pneumothorax (left); inverted cone-shaped shadow in lower lung field (right) with base toward axilla and obscuration of diaphragm

FIG. 3. SAME CASE, DECEMBER 13, 1922

Note improved degree of collapse of left upper lobe, more or less selective; right diaphragm retracted upward, base still clouded and obscured, but the remainder of the lung field has shown clearing

upper lobe and diaphragmatic retraction. Blood Wassermann +++, hemoglobin 60 per cent. Two months of strict bed-rest in the hospital caused no abatement of symptoms, temperature regularly reaching 103°F. Left pneumothorax induced August 12, 1921. Definite symptomatic response, with lowering of temperature. On August 21, following a refill of 450 cc. there was marked febrile and constitutional reaction, temperature 104.2°F. Roentgenograms September 2 (see fig. 2) showed definite extension in right lung in the form of heavy infiltration, extending downward and outward from the hilum in the shape of an inverted cone, its base in the axilla. Fresh râles meanwhile appeared over the right lower back, and later basal dulness, diminished breath-sounds, and crepitations in the lower axilla. As late as April, 1922, a fine friction rub was heard here, and roentgenograms later (see fig. 3) showed a diffuse basal density with marked retraction and fixation of diaphragm. This was interpreted as due to an organized pleurisy, with thickening and adhesions. The parenchymal changes had retrogressed. Pneumothorax had meanwhile been cautiously continued, with small refills at low pressure, and the patient had greatly improved, becoming afebrile and ambulant, with a negative sputum. Vital-capacity readings on several occasions were very low, around 30 per cent of normal. Curiously enough, as the right diaphragm became fixed, the left half (the pneumothorax side) exhibited exaggerated excursions, a thing very unusual in the presence of a pneumothorax, which usually reduces the excursions. The patient was discharged July, 1923, with a fairly collapsed left lung attached by string-like adhesions and one broad band to the lateral wall. A few tubercle bacilli were demonstrable in the sputum. She was dyspneic on exertion, but otherwise felt well.

Case 5198: Male; student; age 18. Admitted May 23, 1923. History of onset, five months before, with undue fatigue, listlessness and loss of appetite, followed by slight cough. Sent away to the country without supervision or directions until April, when he consulted a physician at Liberty, New York, and was put to bed. Meantime he ran irregular fever, had night-sweats, cough and increasing expectoration. Signs of infiltration throughout right lung, most severe in upper, with evidence of cavitation; also slight infiltration decending from left root into lower. Roentgenograms revealed multiple cavities in right upper, otherwise confirmed physical signs. Fingers were clubbed and nails cyanotic and curved. A month of strict hospital care and bed-rest did not influence the fever or course of the disease, and right pneumothorax was induced, June 26, 1923. The upper-lobe cavities were resistant to collapse, and pressure could not be raised because of weak flexible mediastinum. The symptoms, therefore, were not greatly ameliorated. In August, 1923, an effusion appeared in the right chest and accumulated rapidly, necessitating aspiration, which was repeated at intervals. A lessened degree of fever (up to 100 or 101°F.) persisted. Late in November, 1923, patient complained of pains in opposite side of chest, and dyspnea, always noticeable, increased. On November 27 examination of left chest showed dulness from fourth interspace and angle of scapula down, with diminished breath-sounds and a few fine axillary crepitations. Exploratory puncture discovered fluid. Aspiration of 300 cc. was performed with some relief, and later of 650 cc., 250 cc. of air being introduced. Aspiration and occasional introduction of air were repeated at intervals until January 5, 1924, when the pleural layers became adherent. Pneumothorax refills of the right chest were meanwhile abandoned because of the appearance of progressive disease in the left lung and the marked dyspnea and deficient oxygenation, but the right lung never reëxpanded sufficiently to be of any use. The patient grew steadily worse and died March 14, 1924, with symptoms of gradually increasing asphyxia. A well-marked systolic murmur had previously appeared over an area adjacent to the heart apex and gradually increased in loudness and extent. A systolic murmur was also heard over the pulmonic area, the pulmonic second sound was tremendously accentuated, and the area of cardiac dulness increased.

Case 5264:—Male; accountant; age 30. Admitted January 16, 1922. History of sudden onset, two months before, with chills and cough following automobile ride, followed by persistent fever; later bacillary sputum, cough, loss of weight, hoarseness. *Admission diagnosis:* Severe infiltration, with some fibrosis and cavitation right upper; less marked in middle and upper part of lower; questionable signs upper part left upper. Roentgenograms showed dense bronchopneumonic and fibrotic infiltration right upper, cavitation above second rib and pleural thickening; moderate infiltration median half below; a few peribronchial deposits behind fourth rib on left. Complicating tuberculous laryngitis without ulceration was diagnosed. After two months' observation, fever persisting with other evidences of active, progressive disease, a right pneumothorax was induced, notwithstanding the development of a few parenchymatous deposits of infiltration in the left upper lobe. Some benefit was noted, but collapse was restricted by adhesions and by solidified lung about the upper-lobe cavities. The effective intrapleural pressure could not be increased because of a weak, flexible mediastinum, and some fever and troublesome cough persisted. In September a pleural effusion developed in the right chest, with temporary febrile reaction, which subsided and the effusion resorbed. By November, 1922, the patient was afebrile and was moved to a cottage. In December, however, there was an acute flare-up of fever with increased expectoration, and he was returned to the hospital. New roentgenograms showed a well-marked infiltration on the left, extending downward and outward from the hilum, as well as progressive cavitation in the incompletely collapsed right upper lobe. Late in January the temperature rose to 102.8°F., and new signs appeared over a limited area in the left axilla, suggesting a localized infiltration or consolidation, together with a definite pleural friction rub. On February 6, 1923, a new effusion appeared on the right side, causing further mediastinal displacement and dyspnea. Meanwhile dulness developed at the base of the left axilla, with diminished breath-sounds. Dyspnea became marked. On February 12, 300 cc. of air were removed from the right chest. On February 22, the left chest was explored without finding fluid, but 300 cc. were removed from the right chest. Again, March 3, the left chest was explored, 200 cc. dark amber fluid removed, and 475 cc. from the right chest. Three more aspirations were performed on the right prior to March 24th, when a dry tap of the left chest was done. It should be noted that the fluid from both chests showed the presence of tubercle bacilli on guinea-pig inoculation. Shortly afterward pneumothorax was discontinued. Meanwhile the temperature slowly fell and general improvement was shown. Hemoptyses recurred, however, and, together with persistent cough and expectoration and intermittent fever, caused a thoracoplastic collapse of the right chest to be decided on, as the left lung lesion appeared to retrogress slightly. Following operation the patient returned for further treatment and is doing well.

COMMENT

In the first case the contralateral pleurisy evidently developed subsequent to the extension in the corresponding lung, and became manifest chiefly by its end-results, especially retraction and immobility of the diaphragm. Its chief clinical importance seems to have been to diminish still further the vital capacity. Likewise, in the third case there was definite evidence of extension of the tuberculous process in the contralateral lung prior to the appearance of the pleurisy, the latter undoubtedly occurring when this process reached the visceral pleura. The pleurisy itself was of only transient clinical importance, but the

associated pulmonary extension weighed in the decision to discontinue pneumothorax treatment, the benefits of which were but limited. In the second case the pleurisy on the contralateral side antedated the evidence of manifest pulmonary extension, but it seems more than likely that a latent development and extension in the lung was taking place before the pleurisy. The development of the cardiac lesion is a point of interest, and this, together with the inability of the lung first collapsed to be of any use, undoubtedly hastened the end. Here, too, the pleurisy *per se* seemed to be of minor importance. In two of the three cases here reported the presence of a contralateral serous exudate was proved by exploratory puncture. The third was not explored, but from the appearance of the roentgenograms taken afterward the diagnosis of a preceding exudative pleurisy seemed justified.

DISCUSSION OF CASES THUS FAR REPORTED

Of the 16 cases, including our own, which have thus far been reported in detail, the original pneumothorax was on the right side and the contralateral pleurisies on the left in 10, and vice versa in 6. Nearly all had an effusion on the pneumothorax side as well, usually occurring some time prior to the contralateral pleurisy, sometimes disappearing prior to it, in other cases coexisting with it. In one case, that of Lindig, there was also a pericarditis, but recovery ensued. In one of our cases there was a cardiac complication, which contributed to the fatal outcome. The time which elapsed between the institution of pneumothorax and the contralateral pleuritis varied widely,—from 18 days in Lindig's case to nearly three years in one of Pisoni's cases. The effects of the pleurisy *per se* did not appear to have been, as a rule, serious, although some of the patients presented alarming dyspnea, as might be expected, and some a marked cyanosis. Where these symptoms were due solely to the development of the exudate, aspiration afforded prompt relief. The immediate outcome in most seems to have been favorable. Fishberg, Zemmin, Als, Stivelman, and Lindig report good results, but some of their patients were not followed very long. One of L. S. Peters's patients recovered; the other died of unmentioned complications. In two of Pisoni's cases the subsequent course was unfavorable, and all three showed a diffusion of the tuberculous process in the contralateral lung. Our experience has been somewhat similar, all three patients having shown evidence of a definite increase or diffusion of the tuberculous pulmonary process, but despite this two of them subsequently improved,

the other pursuing an acutely progressive course. As for treatment, aspiration was imperative when the effusion was of any considerable amount, but in a few instances small effusions underwent spontaneous absorption. Spengler (3) says that the fluid on the "sound" side must be aspirated as often and freely as the dyspnea requires, the intrapleural pressure on the pneumothorax side meanwhile being kept near neutral.

The character of the fluid in all cases in which it was examined was found to be that of an exudate. In one of our two cases in which the fluid was examined tubercle bacilli were demonstrated by animal inoculation. This would indicate that we have in these pleurisies, just as in the exudates developing on the pneumothorax side, an inflammatory and exudative reaction to tuberculous pleural foci. The frequent demonstration of an accompanying spread of the pulmonary process supports this view. Neuer (4), in her interesting review of pneumothorax complications, suggests that in a pneumothorax pleuritis (homolateral) we have an especially frequent localization of the tuberculous process, and refers to Noetze's experiments indicating diminished resistance of the pneumothorax pleura to pathogenic microörganisms. She likens the fresh outcropping of foci outside the diseased lung to the battle with the hydra, where fresh tentacles appear one after another. In favorable cases the foci remain confined to the pneumothorax pleura; in unfavorable cases they spread to other organs, including the opposite lung. Pisoni's (5) conclusions may be mentioned, as our own experience has led us to very similar ones. He believes that exudative *contralateral* pleuritis almost invariably aggravates the patient's condition and renders the prognosis less favorable, although *per se* its course is often not unfavorable; and that intervention should be directed toward removal of the exudate with the least possible disturbance of the pneumothorax.

CONCLUSIONS

1. Contralateral exudative pleuritis complicating artificial pneumothorax, while very uncommon, is probably less rare than was formerly thought. Its incidence at Loomis has been 1.31 per cent. It is usually associated with or preceded by a homolateral exudate.

2. *Per se*, this complication is not necessarily grave, although the immediate symptoms may be very alarming. It is, however, commonly associated with a progression, of greater or less degree, of the tuberculous process in the corresponding lung, which, if it continues, fore-

shadows an unfavorable outcome. The pleurisy is itself a manifestation of a new tuberculous localization.

3. Aspiration of the exudate is usually imperative and should not be delayed if the dyspnea is pronounced or cyanosis develops. The decision as to continuing pneumothorax treatment, however, will depend on developments in the contralateral lung itself. For the time being the pneumothorax is generally best let alone, or left *in statu quo*.

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AIR EMBOLISM AND ARTIFICIAL PNEUMOTHORAX

Report of a case[1]

H. A. BISHOP[2]

It is not the province of this paper to review in detail the subject of air embolism with relation to artificial pneumothorax but rather to discuss some of the salient points with special reference to its causation, mechanism, frequency and prophylaxis.

In looking up this subject one is immediately impressed by the dearth of literature in the English language, and for this reason it has seemed worth while to report one case with autopsy findings, following the administration of air in an effort to produce artificial pneumothorax.

Case Report

H. G., male, 51 years of age. Spent twenty-eight years in United States Army, with six years of tropical duty. Family history negative as relates to himself. Past history shows that he had been a moderate drinker, but never to excess. Measles and mumps as a child. Frequent colds until about twelve years of age when these apparently ceased. Mild attacks of dysentery and malaria while in the Philippine Islands in 1902, which quickly responded to treatment. While in Siberia in 1918 had a severe cold lasting for about three weeks, during which time he vomited blood. No history of venereal disease.

Present Illness: Illness started with a cold in June, 1923, at which time he coughed considerably. This cough gradually increased and was followed in a few weeks by night-sweats, weakness and loss of weight. Patient believed that he would improve and did not report for care until about a month later. He was sent to Walter Reed General Hospital, diagnosed active tuberculosis, and sent to Fitzsimons General Hospital for treatment. On entering this hospital it was noted that he had continuously lost weight, was easily fatigued, had afternoon temperature ranging from 99° to 101°, had pains in his left chest, and occasionally on the right side. He was diagnosed active pulmonary tuberculosis involving the entire left lung, with some old fibrosed lesions in the right upper lobe. There was present multiple cavitation in the left upper lobe, and nodose lesions throughout the remainder of the left lung. There was evidence of pleuritic adhesions on the left side. X-ray findings bore out this condition and sputum was found to be positive for tubercle bacilli. The general condition was fair, patient considerably under weight, raised about 100 cc. of sputum daily, had frequent afternoon elevations of temperature, and was a semi-ambulant patient on an infirmary ward. After three months' observation it was decided to induce pneumothorax, in an effort to collapse the cavities in the left lung. On November 30, 1923, this

[1] Published by authority of the Surgeon-General, United States Army.

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was started. Because of adhesions, considerable difficulty was encountered in getting an air-space, but after several attempts 200 cc. of air was introduced. From this date fillings were given until January 4, 1924. Only very small quantities of air could be introduced at any one time and some attempts failed.

On January 4, 1924, at 11 A.M., another effort at refilling was made, and difficulty was experienced in locating the pleural cavity with the pneumothorax needle. A number of attempts were made through the same skin-puncture, with unsatisfactory manometer readings. Notwithstanding, it was decided to attempt to introduce a small amount of air as it was considered that the readings indicated a pocket walled off by adhesions. It was believed that at this filling, as previously, a small opening from the pocket might exist, through which air would pass into other pleural spaces. With this in mind 100 cc. of air was introduced under some increase of pressure.

During the administration the patient complained of a burning pain at the site of the operation, which was interpreted as pleural in origin due to pressure on the adhesions. The final manometer reading showed decidedly positive pressure with practically no oscillation. The needle was withdrawn and puncture closed with collodion. The patient then rose to a sitting position, preparatory to leaving the operating room, when he collapsed with total unconsciousness, accompanied by tonic spasms of the muscles of the right side of the face, extensors of back and lower extremities, and tonic spasm of the diaphragm and abdominal muscles, causing extreme cyanosis. His head was immediately lowered. Conjugate deviation of the pupils to the right accompanied the right facial spasm.

It might be well to emphasize the point that this train of symptoms began at the time of his sitting up on the table, and not during the introduction of air. The tonic spasms were followed by clonic spasms in all muscles previously affected, but tonic spasm of the diaphragm did not relax long enough to permit of adequate respiratory movements, and death seemed imminent. Pulse was of good character but rapid. Conjunctival reflexes were abolished. Pupillary reflexes were not present, but a decided hippus manifested itself. Artificial respiration was instituted, and 0.65 mgm. of atropine sulphate was given hypodermically. In about five minutes spasms ceased and respiratory movements again became automatic, with a consequent clearing of cyanosis.

Patient was then removed to his bed. His respiration was about 40, extremely stertorous, pulse 140, regular and strong. A deep coma with profuse perspiration existed. Tonic extensor spasm of the lower extremities again became manifest. The deep reflexes of the upper extremities became universally exaggerated with double wrist clonus. At the same time all of the superficial reflexes were abolished. From this time on the patient had syndromes about every half-hour similar in character to the first attack which necessitated artificial respiration. Pulse and respiration gradually became more rapid. At 1 P.M. an ophthalmoscopic examination was made with negative findings. Following this the foot of the bed was raised and 0.5 cc. of 1/1000 adrenalin chloride was given hypodermically. In about five minutes all localizing symptoms changed, and there were clonic spasms of the left arm and leg, with head turned to left and with left conjugate deviation of the pupils. The spasms became more violent and closer together. After about five such attacks patient seemed better, and respiration became slower and less stertorous with no change in the deep coma. From about 5 P.M. until midnight convulsions were at half hourly intervals. From midnight on they became much more numerous and more violent in character.

The following morning spasms were spaced at ten-minute intervals, but the regions involved had changed to such an extent that former ideas as to localization were manifestly erroneous. Spasms were now clonic, and affecting the right arm and leg and the left side of the face, with left conjugate deviation of the pupils, the crossed type of involvement

suggesting a pontile irritation. Pulse had become weak and very rapid. Blood pressure showed *S.* 56; *D.* 42. Patient had twenty-four convulsions between 7 A.M. and 3 P.M., when death ensued.

The extreme irritability of muscles with convulsions is believed to have pointed to a cortical or meningeal irritation, or both, with air emboli moving in superficial vessels of cortex around the anterior Rolandic area and possibly in the basal vessels.

Two theories as to the wide distribution of the changing neurological symptoms, covering a period of approximately twenty-eight hours, might be offered. That the cerebral irritation was of extreme degree and ever present from the inception of symptoms until death ensued cannot, we believe, be disputed, and was due to either an enormous initial single intake of air into the vascular system, being later broken up into numerous smaller bubbles, or air was being drawn constantly in small quantities into the circulation from the pneumothorax pocket. The needle evidently punctured or transfixed a vein, which on account of fibrosis in or around the vessel could not collapse after the needle was withdrawn, and air was aspirated into the vein. Before leaving the symptomatology, comment on the negative ophthalmoscopic findings might be in place. It will be recalled that a fundus examination was not made until about two hours after symptoms began. A review of the literature shows that even in experimental cerebral air embolism, in which bubbles may be seen in the retinal vessels, this phenomenon usually takes place early, and may be very transient.

After death there was an autopsy performed within two hours, and the following pathological findings are quoted from report of necropsy: *Lungs and Pleura:* The left pleural cavity was almost completely obliterated by dense old fibrous adhesions. These were dissected with a knife, in order to note any air-pocket of pneumothorax that might be present. An area about the size of an egg was found in the interlobar fissure in the axillary line. As this was smooth and free, and as the entrance of the needle was in this area, it was felt that this was probably the pneumothorax pocket. It was not believed to be of a volume equal to the amount of air introduced. In the back, the pleura was about ¼ inch thick, white and very fibrous. The upper lobe of the lung was very firm, tough and nodular. The lower lobe showed some crepitation, and nodules were palpable throughout. On section, the upper lobe showed old anthracosis and fibrous nodose lesions of tuberculosis. There were some caseated areas in some of these. There were also a few small cavities in the apex. These were surrounded by dense fibrous tissue. The bronchi and bronchioles were all wide, and distended with thickened walls showing marked bronchiectasis.

The heart and mediastinal contents were drawn to the left, due to contraction. The right lung was comparatively free, except about the apex, where it was quite firmly adherent. The same old fibrous nodose lesions were palpable in the upper and midlobes. None were definitely palpable in the lower. On section, nothing more was found in this lung. *Heart and Pericardium:* The pericardium showed nothing externally, except the adhesions noted above. The heart was enlarged, and the ventricles slightly thickened. The valves were clear. The aorta showed numerous fatty atheromatous plaques. There was no evidence of syphilis. In the apex of the left ventricle there was quite a large hemorrhagic area in the musculature. The source and cause were not found. *Abdomen:* The viscera were in normal relationship. The intestines were adherent in numerous areas throughout the entire length. On being opened, the intestines showed some mural thickening in the caecum and lower ileum and a few ragged ulcers apparently fairly recently formed. The ulcers were quite evidently tuberculous and the thickening probably due to an old bacillary dysentery while in the tropics. The liver, gall-bladder, spleen, pancreas, adrenals, and kidneys showed no evidence of pathological changes. *Cranium:* The head was opened in this case because of the diagnosis of cerebral embolism. The skull-cap was carefully

sawed, in order not to tear the dura. Only a slight nick in the dura was made in the left side above the ear. The external vessels of the dura were pale and almost bloodless. Beneath the dura the vessels were congested and distended. The dura was carefully cut with scissors and removed. Over the summit it was very adherent and there appeared to be some exudate. There was fairly well marked edema of the whole surface of the brain. The exudate was smeared and stained but no microörganisms were found, a few polynuclear cells being present. On the left side the vessels were full of blood. On the right side the vessels were filled with air bubbles. As the most extreme care was used in removing the dura, it is felt that none of these vessels were injured, and that the presence of air was due to the presence of air in the circulating blood at the time of death. The external vessels of the medulla and the base of the brain were engorged with blood. Section of the brain failed to show anything except vascular congestion. There were no hemorrhages present.

Combining the clinical and postmortem findings we find the following pathological changes present: (1) Tuberculosis, pulmonary, chronic, both lobes left, right upper and midlobes; fibrous nodose lesions predominating; small multiple cavities left upper. (2) Pleuritic adhesions, and pleuropericardial adhesions left. (3) Bronchiectasis left lung. (4) Cerebral air embolism. (5) Cardiac hypertrophy, moderate. (6) Hemorrhage in apex left ventricle. (7) Intestinal adhesions, chronic. (8) Enteritis, chronic, tuberculous, ulcerative, lower ileum and caecum.

A retrospective study of this case emphasizes certain points:

1: The case was one with extensive pleural adhesions, the type of case in which artificial pneumothorax treatment is dangerous and difficult on account of unsatisfactory manometer readings and the liability of introducing the needle into the lung or transfixing a vessel in a highly vascularized pleura.

2: Attempts at inducing pneumothorax produced only a small air-pocket surrounded by dense adhesions, which were firm and impossible to separate.

3: After a number of refillings, when air was introduced under slightly positive pressure, it gave the train of symptoms described above.

4: These symptoms were associated with the withdrawal of the needle.

5: The symptoms were characteristic of cerebral air embolism.

6: The only pathological evidence of cause of death was the presence of air in the cerebral vessels at autopsy.

7: This air may have been aspirated into the vessels at autopsy even though every precaution was taken to prevent this from happening.

The causes of air embolism incident to artificial pneumothorax naturally fall into predisposing and direct, and all writers unanimously agree that cases with marked pleuritic adhesions are predisposed to such accidents. The explanation, however, remained for Schlaepfer, who showed by animal experimentation that chronic pulmonary congestion

and pleural adhesions cause an increase and enlargement of collateral circulations in the pleura, thereby facilitating entrance of air into these vessels and thence into the general circulation.

The direct cause of embolus is manifestly the entrance of air into a pulmonary or bronchial vessel. The mechanism of such entrance varies and may be due to:

1: Rupture of a vessel of an alveolus, opening a communication between alveolus and a pulmonary vein. This is most likely to occur in those cases in which the pleural space has been obliterated, and the needle is plunged directly into lung tissue, especially if some pathological process, such as bronchopneumonia or fibrosis, be present in this area, and prevent the transfixed vessel from contracting and obliterating the opening.

2: Air may pass directly from the needle into a pulmonary vein or an engorged vessel of the diseased pleura.

3: Air may pass into a transfixed vessel of the pleura after the needle is withdrawn, fibrosis in and around the vessel preventing contraction. The blood supply of the lung being unique, because of the function of this organ, when air enters into one of its vessels it may pass either into the right or left heart, the train of symptoms varying accordingly.

Statistics as to the incidence of air embolism following induced pneumothorax vary from 1 in 1,000 to 1 in 1,500; but it is believed that, as operators become more and more on the alert and more familiar with the signs of minor embolic processes, especially extracerebral emboli, a revision of these figures will ensue. In this connection it may not be amiss to mention, in passing, two other cases occurring on the same infirmary ward as the case reported, which symptomatically gave evidence of embolic air in the vessels.

Both of these cases had extensive adhesions and were discontinued after a few attempts in which it was possible to introduce only small quantities of air, because we felt that no benefit could be derived from continuance. The symptoms shown in these two cases were very much alike, occurring immediately after withdrawal of the pneumothorax needle. They complained of some pain in the right shoulder, and immediately following this complaint, blindness, lasting in one patient for a period of some five or ten minutes, in the other case for about thirty minutes. The first one returned to normal after a brief interval, while the other complained of some dizziness on the slightest exertion during the ensuing twenty-four hours, and a moderate headache for a period of about three days. No

immediate retinal examinations were made; hence there was no pathological evidence present to prove or disprove these cases. Such occurrences have kept us more sharply on the lookout for mild and temporary symptoms, and lead us to the belief that a slight embolus of air may be present in these pneumothorax cases more often than we would ordinarily suspect, were they not especially watched for.

The prognosis depends on many factors. The mortality rate is high, varying from 30 to 50 per cent, according to most writers. However, in this instance figures are misleading, as the personal equation and diagnostic acumen of the investigators may cause wide variations. Here again it is thought probable that statistics will be revised as more of the minor cases are recorded.

The treatment is symptomatic and in the severe cases discouraging. Prophylaxis holds out the greatest hope. Cases with adhesions should always be approached cautiously, and only after careful physical and X-ray study. Air should not be introduced until a negative manometer reading is obtained and definite oscillations are present. Surface areas over consolidated lung should be avoided as the point of election if possible. The location of the needle should definitely be known before starting to introduce air. Often the cannula inserted, withdrawn and wiped on clean gauze will indicate an injured vessel. Introduction of air should immediately cease on the slightest sign of trouble, either subjective or objective. Every case should be X-rayed at regular intervals before refillings. The fluoroscope will suffice. Only in this way can we keep a careful check on the position of the collapsed lung and the position of adhesions.

In closing, may I emphasize the fact that the induction of artificial pneumothorax is essentially a surgical procedure and, as such, is not wholly devoid of danger and may at times, even despite our most painstaking precautions, be fraught with most dramatic consequences.

STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE

XX. THE VALUE OF THE VITAL-CAPACITY TEST IN ARTIFICIAL-PNEUMOTHORAX TREATMENT[1,2]

J. A. MYERS AND WILLIAM BAILEY

Attention has been called to the fact that pneumothorax has a very definite effect upon the vital capacity of the lungs. In a group of 9 cases (1) the capacity ranged from 32 to 58 per cent, while the average was 49 per cent of the theoretical normal. Obviously the extent of the collapse present and the condition of the uncollapsed lung-tissue will determine somewhat the vital capacity.

Means and Balboni (2), after making a careful study of the various factors of respiration in 4 persons with artificial pneumothorax and one with spontaneous pneumothorax, arrived at the following conclusions:

> It may be said that at rest all the factors of respiration, gaseous exchange, carbon dioxide tension, and the mechanical factors, are normal in persons with a collapsed lung, that the reaction to carbon dioxide is normal up to the point at which the respiration is trebled, or sometimes quadrupled, but that beyond that point a limit may be reached.
>
> The ventilation of the lungs can be accomplished in an entirely normal manner in spite of a greatly reduced vital capacity. The only difference between normal persons and persons with a collapsed lung is that the latter when called upon to increase their ventilation reach their limit a little sooner than the former.
>
> From these findings we might deduce that there will be no dyspnea except after moderate exertion. And this deduction is borne out by the histories of the patients.
>
> In other words, in the lungs, as in other organs, there is a large factor of safety, one lung being as efficient as two, except when the work done calls for more than a threefold increase in the normal ventilation.

Our report includes 2 cases of complete spontaneous collapse, 3 cases of partial spontaneous collapse, 8 cases of artificial collapse on which only one reading was secured, and 11 cases of artificial collapse on which several readings have been taken before and after artificial pneumothorax treatments, and 4 cases on which readings have been taken routinely

[1] From the Department of Preventive Medicine and the Department of Internal Medicine, University of Minnesota, and the Minneapolis General Hospital.

[2] This study was carried out with the aid of a grant from the Research Fund of the University of Minnesota.

before and after each treatment since beginning artificial pneumothorax. This report also includes two cases on which extrapleural thoracoplasty had been done.

In one case of complete spontaneous collapse of the left lung the vital capacity was not taken until a few days after symptoms had disappeared and the lung had partially reëxpanded. At this time the right lung appeared clear. The vital capacity then was 3300 cc. which was 81 per cent of the theoretical normal.

A young woman with complete spontaneous pneumothorax on the left side and extensive fibrous tuberculosis of the right upper lobe presented a vital capacity of 32 per cent of the theoretical normal. A case with a partial spontaneous pneumothorax at the left base and fibroid tuberculosis of both upper lobes had a vital capacity of 77 per cent of the theoretical normal. Another case with a small localized pneumothorax at the left base and fibroid tuberculosis at the left apex also had a capacity of 77 per cent of the theoretical normal. A man of forty-four years, with fibroid tuberculosis of both upper lobes and a partial spontaneous pneumothorax on the right side, presented a vital capacity of 51 per cent of the theoretical normal. In the above cases except the first it is impossible to determine just what part the pneumothorax played in reducing the vital capacity, inasmuch as other conditions were present which were capable of reducing it.

In the following group of cases only one reading was taken:

A man of thirty-seven years who had suffered from chronic pulmonary tuberculosis for many years was given artificial pneumothorax. At the time the vital capacity reading was taken there was an extensive tuberculous lesion involving the entire left upper lobe with a partial pneumothorax at the level of the third to the fifth ribs in the midaxillary line. At this time the vital capacity was 54 per cent of the theoretical normal.

A man of twenty years with tuberculosis of the left lung had artificial pneumothorax begun in the summer of 1921. In March, 1922, when the left lung was well collapsed and the right lung appeared clear, his vital capacity was 48 per cent of the theoretical normal.

A man of thirty-three years was told that tuberculosis existed in the left lung in October, 1920. In August, 1921, pneumothorax was induced. In August, 1922, just before a treatment, the left lung was somewhat reëxpanded and the vital capacity was found to be 65 per cent of the theoretical normal.

A woman of twenty-five years with disease of the left upper lobe had been taking artificial-pneumothorax treatment for five months, when her vital capacity was found to be 66 per cent of the theoretical normal. Although her right lung was clear pleural adhesions prevented a complete collapse of the left lung.

A man of twenty-nine years had been treated for pulmonary tuberculosis for seven years, the last three of which had been by artificial pneumothorax. At the time the vital capacity reading was taken, the right lung was found to be almost completely collapsed while the left lung was clear. The vital capacity was 58 per cent of the theoretical normal.

A woman of thirty-seven years was given artificial-pneumothorax treatment after having suffered from pulmonary tuberculosis for five years. The right lung was entirely collapsed, but disease was present in the left upper lobe, when the vital capacity was found to be 26 per cent of the theoretical normal.

A man of twenty-seven years developed tuberculosis of the right middle and lower lobes, after which pneumothorax was induced. Several months later when he was ambulatory the right lung was found to be almost completely collapsed and the left lung was clear. His vital capacity was 51 per cent of the theoretical normal.

A woman of twenty-nine years developed tuberculosis of the left lung with pleural effusion. After the usual treatment had failed the fluid was partially removed and replaced with air. At the time the vital capacity reading was taken, the examination revealed a hydropneumothorax on the left side. The right lung was clear. At this time the patient's vital capacity was 51 per cent of the theoretical normal.

A man of thirty-three years developed a small tuberculous lesion in the upper lobe of the left lung. His vital capacity was then 3600 cc. (chart 1). He then went to a sanatorium where he apparently did very well and was later discharged to return to work. In August, 1922, he relapsed. At this time his vital capacity was found to be 3300 cc. He was admitted to another sanatorium, where, after six months, artificial pneumothorax was begun. In August, 1924, while still on pneumothorax treatment, his vital capacity was found to be 2400 cc. (chart 1).

In a group of 11 cases artificial pneumothorax was in progress before we began to make vital capacity readings a routine procedure. In this group of cases we have been interested in determining how much a given amount of air injected into the pleural cavity reduced the vital lung capacity. In order to determine this we have taken the vital lung capacity immediately before and immediately after the pneumothorax treatments. In almost every instance we have found that the vital capacity reduction is not equal to the amount of air injected into the pleural cavity. For example, one patient who had pneumothorax treatment over a period of more than two years was found to have a vital capacity of 2500 cc. just before a refill; 500 cc. of air was injected into the pleural cavity, after which her vital capacity was found to be 2100 cc. At a later time her vital capacity was 2300 cc. before an injection of 400 cc. of air. Her capacity was reduced to only 2150 cc. In all of our cases the amount of air injected into the pleural cavity was determined by the manometer reading. When this reading reached zero or became very faintly positive the injection of gas was discontinued. There was only an occasional case with very extensive adhesions in which only a small pocket of air could be injected. When we used definitely positive pressure in such cases the amount of pressure used apparently had very little effect on the vital capacity.

One occasionally meets with a patient who has very extensive pleural adhesions; indeed, the visceral and parietal layers of pleura may be almost

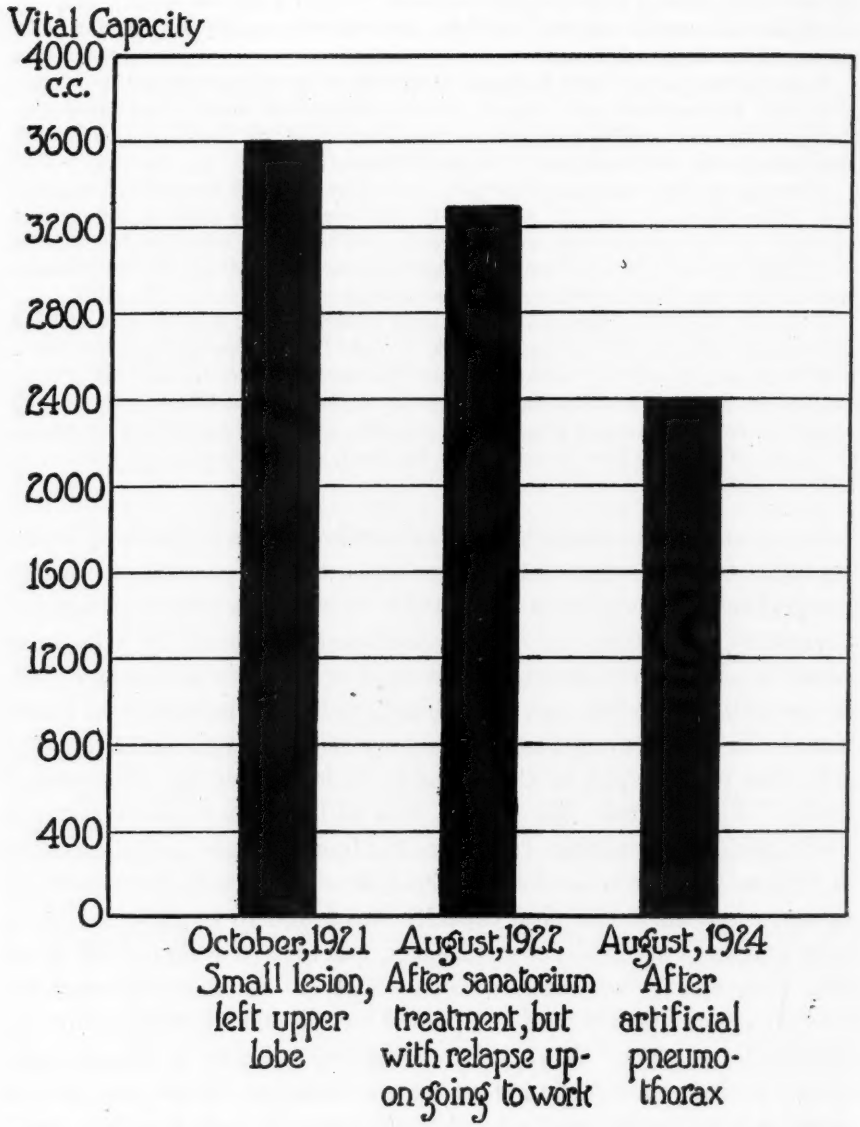

CHART 1. SHOWS DECREASE IN VITAL CAPACITY CAUSED BY INCREASING PULMONARY TUBERCULOSIS

In the last column the marked decrease resulting from artificial pneumothorax is shown

completely adherent. In such cases the needle may pass through the visceral pleura into the lung without the operator being aware of the presence of adhesions. The oscillations on the manometer may be slight and the inexperienced operator may introduce air directly into the lung. Good-sized quantities may be recorded, and without X-ray control the operator may believe that the air has reached the pleural cavity. In such cases the vital capacity taken just before and just after an artificial-pneumothorax attempt will furnish one with much information. One will find that, although 400 or 500 cc. of air have passed through the needle, the patient's vital lung capacity has not decreased. This error should be avoided because the negative pressure on the manometer will in most cases inform one as to the location of the needle. However, the inexperienced operator may be misled by slight oscillations when the needle is within the lung tissue.

In another group of 4 cases we have been able to follow the vital capacity readings throughout the course of pneumothorax treatment. Chart 2 shows that a patient with a vital capacity of 3200 cc. before the initial pneumothorax treatment presented a vital capacity of only 2300 cc. after the first injection of 250 cc. of air. Although this did not occur in each case it seemed to be a fact of considerable significance; for example, if one is dealing with a patient who has a very low vital capacity, even by the introduction of a small amount of air the vital capacity may be reduced so as to approach the tidal air. Obviously such patients would suffer much dyspnea and discomfort. Therefore the vital capacty taken before the initial injection of air may be found of great value in determining the amount of air which can safely be injected. After the first treatment chart 2 shows that subsequent injections reduced the vital capacity only slightly and never to the extent of the amount of air injected. Therefore, if the patient has a low vital lung capacity, an amount as small as 50 or 100 cc. of air may be introduced and repeated within twenty-four hours.

In one patient who had a vital capacity of only 1000 cc. before artificial-pneumothorax treatment was begun, marked dyspnea was experienced after the injection of approximately 175 cc. of air. We feel that it would have been much better and safer to have injected no more than 50 or 75 cc. at first in this instance.

Apparently the extent of involvement in the good or better lung affects considerably the reduction of vital capacity; for example, chart 3 shows graphically the effects of artificial pneumothorax upon vital capac-

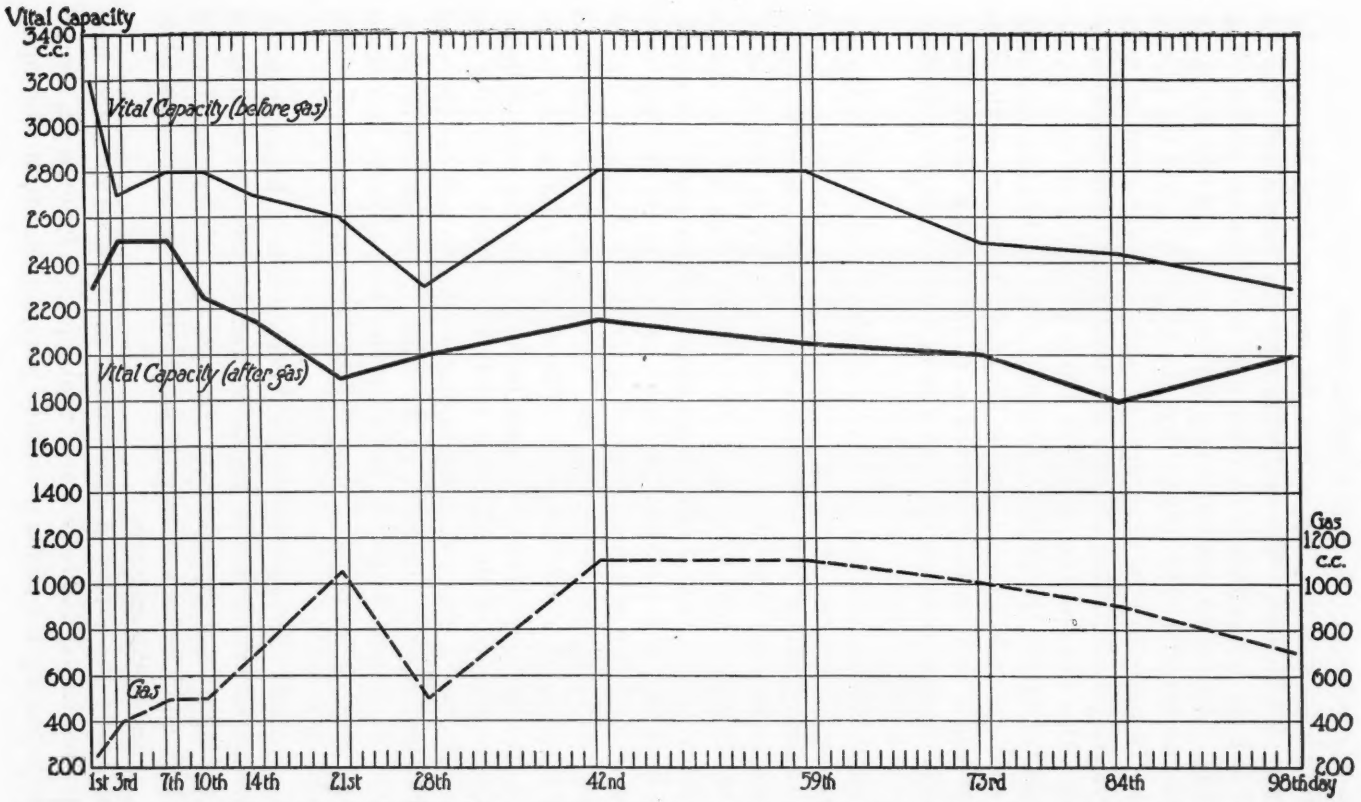

CHART 2. SHOWS VITAL CAPACITY BEFORE AND AFTER ARTIFICIAL-PNEUMOTHORAX TREATMENTS TOGETHER WITH AMOUNT OF GAS ADMINISTERED EACH TIME OVER A PERIOD OF NINETY-EIGHT DAYS

Note the marked decrease in vital capacity following the initial treatment

ity in a patient who had extensive disease on one side with no active process on the opposite side. In this case the injection of gas, bringing about a collapse of the badly involved lung, in the beginning affected the vital capacity only very slightly. It would appear that in such cases the compensatory action of the better lung had already been well established before artificial pneumothorax was begun.

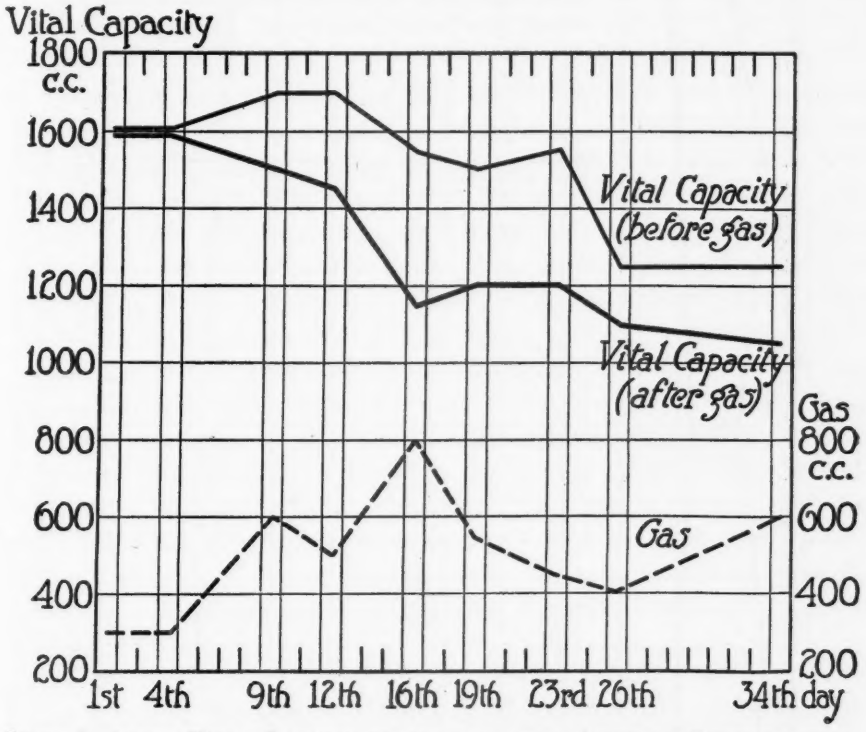

CHART 3. SHOWS VITAL CAPACITY BEFORE AND AFTER ARTIFICIAL-PNEUMOTHORAX TREATMENTS TOGETHER WITH AMOUNT OF GAS ADMINISTERED EACH TIME OVER A PERIOD OF THIRTY-FOUR DAYS

Note the slight effect of the first injection of gas upon the vital capacity

Chart 4 illustrates a case with moderate disease on one side and slight disease on the opposite side. Here we find no marked initial decrease such as is recorded in chart 2.

We have also felt that routine vital capacity readings are valuable in determining the condition of the better lung. In cases with one lung well collapsed we have found that the readings after the injection of air sufficient to bring the manometer reading to zero were quite constant from time to time. Thus, a patient with a vital capacity of 2500 cc.

Note the marked decrease in vital capacity following the initial treatment

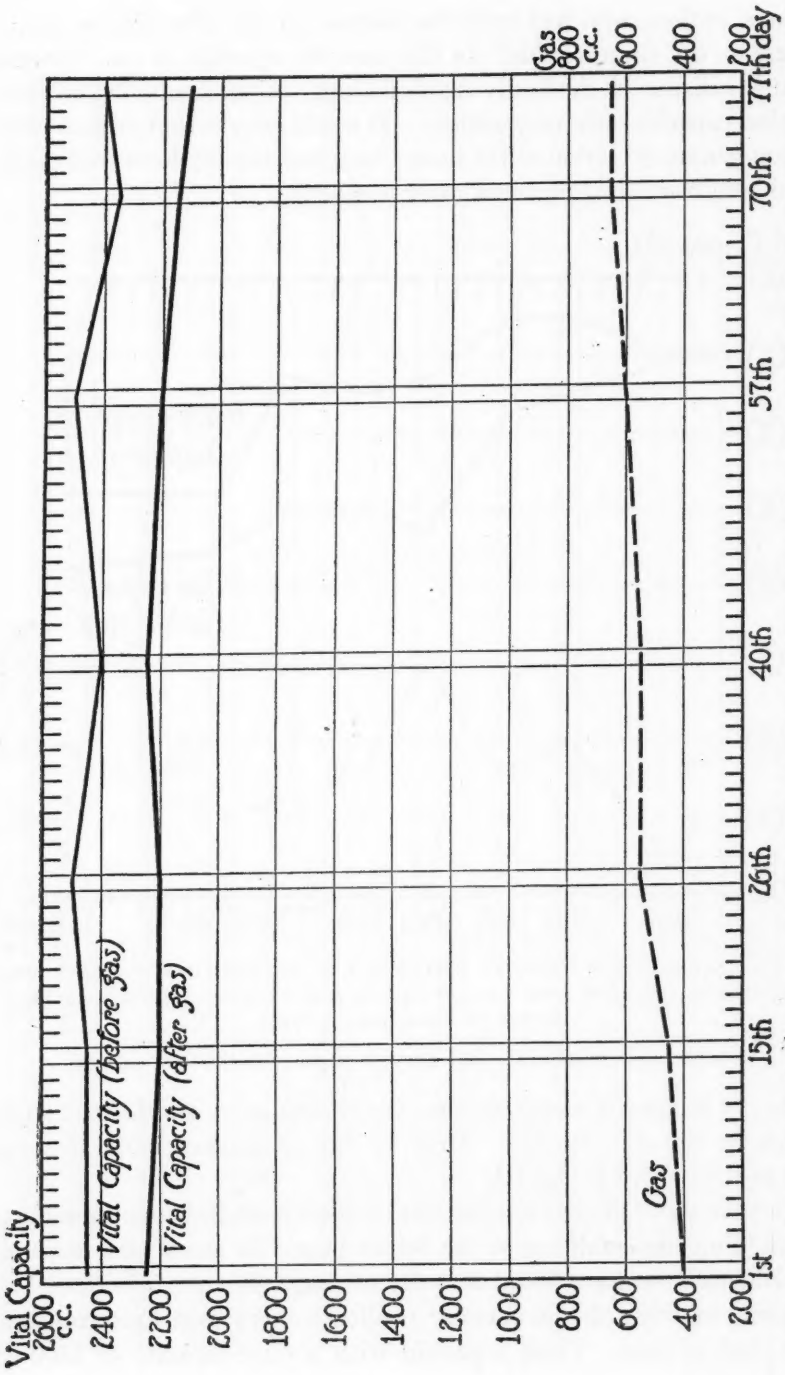

CHART 4. SHOWS VITAL CAPACITY BEFORE AND AFTER ARTIFICIAL-PNEUMOTHORAX TREATMENTS TOGETHER WITH AMOUNT OF GAS ADMINISTERED EACH TIME OVER A PERIOD OF SEVENTY-SEVEN DAYS

after one treatment will have approximately the same vital capacity after subsequent treatments, provided the opposite lung is holding up well. In cases in which the opposite lung is showing definite extension of the disease this is not true but, on the contrary, the vital capacity shows a gradual reduction from time to time.

Graham (3) arrived at the following conclusions:

> Extensive thoracoplastic operations result in apparently a permanent marked reduction in the vital capacity. They should be employed, therefore, only in the rarest instances and only after other methods have been given an intelligent trial for at least many months.

Although our group of cases includes only two that had extrapleural thoracoplasty, they have very definitely borne out this statement. One of these patients, who had an extensive process in the left upper lobe, had been on artificial-pneumothorax treatment with exceedingly good results. This was at the time when it was believed that pneumothorax should not be continued over a very long period. Her physician considered her lung as healed and allowed it to expand completely. The following winter she contracted influenza, following which her tuberculous process became reactivated. Although artificial pneumothorax was attempted many times after this, it was impossible to inject more than 150 cc. of air at any time because of adhesions. Her vital lung capacity was found to be 1200 cc. Since that time she has had extrapleural thoracoplasty in three stages. Segments of all the ribs on the left side above the eleventh were removed. Now her vital lung capacity is only 800 cc. Nevertheless, she has at the present time an excellent working capacity and shows no tendency toward dyspnea as long as she does light work.

In the second case, unfortunately, no vital capacity reading was recorded before the extrapleural thoracoplasty was done. This operation was performed under local anesthesia in two stages. Segments of all the ribs above the eleventh were removed. At the present time this patient's general condition is excellent, yet her vital lung capacity is 1400 cc., which is 45 per cent of her theoretical normal.

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THE SUSPENSION STABILITY RATE OF ERYTHROCYTES IN PULMONARY TUBERCULOSIS AND ITS SIGNIFICANCE IN ARTIFICIAL PNEUMOTHORAX[1]

KARL FISCHEL[2]

Many new methods in the healing art, both diagnostic and therapeutic, which have been hailed with enthusiasm as new discoveries, have been found to be rediscoveries of facts known and forgotten long ago, observed again independently by modern investigators and reappearing with a new meaning and in a new light.

Fahraeus, who published in 1918 his monograph on the suspension stability rate of the blood, was unaware that the hastened settling of the inflammatory blood was known to Galen, who described the *crusta phlogistica;* that this fact was known to the physicians during the Middle Ages and mentioned in the English and German text-books of the first half of the nineteenth century; and that, as far back as 1797, Hunter had tried to exchange the red cells and plasma of different patients, an experiment repeated nowadays with modern laboratory methods by many investigators of the phenomenon of sedimentation. This however does not lessen the merits of Fahraeus, who not only independently discovered and studied the suspension stability rate of erythrocytes under different conditions, but devised the first practical method, and elucidated all the factors which influence the sinking speed of the red cells in blood rendered incoagulable by sodium citrate.

In an age of colloid chemistry of the blood his findings were bound to attract general attention, and for the last five years extensive research work has been carried out on this subject, mostly by German writers, with the result that this simple and useful laboratory test has been studied from all angles. Its importance, as an excellent aid to the methods of diagnosis and prognosis in different pathological conditions, has been generally recognized, and a few plausible theories, which do not conflict with one another, have been developed to explain this interesting phenomenon.

[1] Read before the Foothill Medical Society of Monrovia, California, May 21, 1924.

[2] Jewish Consumptive Relief Association Sanatorium, Duarte, California.

As a résumé of the exhaustive scientific studies, which have been carried out, the following short abstract can be given about the practical results and the theories that are at present accepted by the most experienced observers of the sedimentation test. In blood which is rendered incoagulable by sodium citrate the red cells settle with a speed that is pretty constant in the same individual, but which is subjected to considerable variations under certain physiological and pathological conditions. After a certain time, in normal citrated blood usually after one hour, in many pathological conditions which are distinguished by high values of sedimentation in ten minutes, we can observe an upper layer of clear plasma separated more or less sharply from the red lower layer, containing all the erythrocytes, which have descended toward the bottom. By measuring the height of the clear layer after a certain time (Fahraeus, Westergren, Geppert), or by observing the time which elapses until the maximum of sedimentation is reached (Linzenmeier, Loehr), the sinking velocity of the red cells is determined.

Values of from 3 to 5 mm. for the first hour in men (Westergren, 1 to 3) and from 6 to 8 mm. in women (Westergren, 3 to 7; Hasselhorst, 5 to 12) are generally considered normal, whereas the normal sedimentation time for the newborn is 1500 minutes (Gyorgy), for healthy men between 1200 and 1400 minutes, for healthy women from 800 to 1000, during menstruation sometimes 600, in the climacteric stage prolonged to from 1200 to 1400 minutes (Linzenmeier, Loehr). Compared with the values in healthy men, the suspension stability is increased physiologically in women, the newborn, in old age, during menstruation, and during pregnancy, beginning from the fifth month of gestation and steadily increasing up to the time of delivery. The sedimentation is increased in various pathological conditions, such as in all inflammations, tuberculosis (Westergren, Dreyfus and Hecht, Katz, Katz and Rabinowitch, Graefe, Starlinger), carcinoma and sarcoma (Loehr), syphilis (Popper and Wagner), progressive paralysis, tabes and arteriosclerosis (Plaut), anemias of all kinds, especially pernicious anemia (Linzenmeier, Bloch and Oelsner), malaria (Hirschfeld), and severe affections of the kidneys (Opitz and Frey). On the other hand, a diminished suspension stability was found in cases of icterus and affections of the liver (Abderhalden), and in cases of extreme cachexia, amenorrhoea, insufficiency of the heart with cyanosis (Leendertz), tuberculous meningitis (Opitz and Frey), and polycythaemia.

It will be noted that all diseases and conditions distinguished by

increased sinking values have this in common, that they are associated with destruction of body tissues. The increased suspension stability is not specific for any disease; it is simply, as Waugh puts it, more an expression of a state than a characteristic test. It is a symptom of breaking down of tissue cells and is, therefore, observed in all wasting diseases. For this reason it was soon studied in pulmonary tuberculosis, and recommended by various writers as a welcome addition to our methods of prognosis and differential diagnosis in doubtful cases. Westergren has shown that high sedimentation values are found in active cases and that there is a marked parallelism between the constitutional and other symptoms of activity and the increase in the sinking speed.

Katz studied the relationship of pulse and temperature with the velocity of sedimentation, and has shown that increased velocity is found mostly in febrile cases with a higher pulse rate. Normal values prove, according to Katz, that the process is latent or that there is no tuberculosis at all. While an increased sedimentation is not necessarily an early symptom of pulmonary tuberculosis, it speaks for tuberculosis, if other organic diseases can be excluded, whereas Moral comes to the conclusion that a normal sinking rate does not rule out tuberculosis. Normal or slightly increased sedimentaion is, according to this writer, without prognostic value in incipient cases; in advanced tuberculosis, however, it permits a favorable prognosis, whereas a highly increased sedimentation is a bad sign. Dreyfuss and Hecht point out that higher values indicate a destructive process in the lungs and that the increase is higher in cases with cavity formation than in corresponding forms without cavitation.

Graefe has shown that the sedimentation speed is increased by provocative injections of from 0.03 to 0.3 mgm. of old tuberculin in incipient or slightly active cases, whereas it is not influenced in old healed lesions or healthy persons. He concludes that this sedimentation reaction is more sensitive and appears before any general, focal or local reaction, and has recommended the Fahraeus test as a means of differential diagnosis between latent and active tuberculosis. Poindecker and Sies too are of the opinion that the question as to the activity can be decided by the sedimentation stability, and Rokay shares their views with regard to tuberculosis of the hilar lymph nodes in children.

Finally, Levinson, one of the few American investigators, who have occupied themselves with the sedimentation test, has carried out a comprehensive research on over 400 patients in the various stages of

pulmonary tuberculosis, from the wards of the City of Chicago Municipal Tuberculosis Sanitarium. He considers the sedimentation test as a useful and simple aid to the methods of diagnosis and prognosis of tuberculosis, and one which runs parallel to the degree of anatomic involvement of the lungs and throws light on the activity and progressive nature of the tuberculous process. The speed of sedimentation in early and moderately and far advanced cases shows marked differences in the first two hours, and cavity cases show a greater increase in rapidity of sedimentation than corresponding forms without cavity. Levinson, in his careful study, on the whole corroborates the findings of the authors quoted above.

Tuberculin is not the only means by which we can influence the sedimentation velocity, and we have to take all factors into consideration which increase or lessen the sinking speed, if we want to obtain reliable results. That women, during menstruation, show higher values has been mentioned above, and the tests in female patients should therefore be made between the menstrual periods. The reports on the influence of the intake of food are conflicting (Loehr, Josefowitz). Certain drugs, such as adrenalin, pilocarpin and physostigmin, do not exert any influence (Loehr); likewise variations at different times of the day were not observed (Loehr). The temperature of the room, however, in which the tubes are placed influences the sinking velocity to a great extent; as high temperatures increase it, low temperatures retard it. Injection of serum, caseosan and colloidal silver, and X-ray and radium irradiations and the addition of cholesterin (Starlinger) accelerate sedimentation, and the opposite result is obtained if lecithin is added to the blood. The observations of Caspari, Eliasberg and Fliegel on the influence of serum injections are especially interesting. These authors found that the sedimentation speed of the blood does not show any change for the first ten days. About the twelfth day a sudden change takes place, which lasts one day only and coincides with the serum disease. These observations seem to support Widal's theory, that the real nature of anaphylactic shock is a disturbance of the balance of the plasma colloids.

THEORY OF SEDIMENTATION

Many authors have interested themselves with the explanation of the suspension stability, and several theories have been developed by Fahraeus, Linzenmeier, Mond, Pewny, Vorschuetz, Bloch and Elsner.

Hoeber had prepared the field for Fahraeus's original electrical theory

by having shown, in 1904, that the erythrocytes wander to the positive pole and are therefore charged with negative electricity. If the iso-electric point (point of neutrality) of a slowly sinking erythrocyte suspension is determined by means of the very positively charged lanthanum, it is found that it requires a higher concentration than is required to bring a rapidly settling suspension to the iso-electric point, where the red corpuscles carry neither a positive nor a negative electric charge. Fahraeus and Hoeber therefore concluded that the rapidly settling blood contains an electro-positive substance, which deprives the red corpuscles of their negative electric charge and causes them to cling to each other instead of repelling each other, as in the normal blood, and thus to sink to the bottom more quickly on account of their greatly diminished surface. Tokujiro states that any reduction of the sedimentation depends on an increase, any acceleration of the sinking velocity on a diminution of the negative electric burden.

As the rapid sedimentation is invariably associated with a relative increase in the globulin fraction and a decrease in the albumin fraction (Hoeber, Fahraeus), the globulins probably play the most important rôle. Fahraeus later substituted his electrical by a physico-mechanical theory, by admitting that the viscosity may be an important factor in the production of the rapid sedimentation, whereas Hoeber now assumes that the albumins, in the adsorption envelope of the red corpuscles are more or less replaced by globulins, which have a higher iso-electric point. Starlinger, basing his idea on Klinger-Herzfeld's theory, believes that an increase of polypeptides in the adsorption envelope of the erythrocytes is the cause of the increased sedimentation. Mond states that the influence of the blood proteins on sedimentation depends on their iso-electric point and on the stability of their electric charges.

Now, the degree of viscosity of protein solutions is indirectly proportional to their electric burden, as globulins have a very high and albumins a low viscosity, and for this reason a high globulin level will cause a rapid agglutination, both by the greater viscosity of the globulins and by the diminution of the electrical charges of the red corpuscles. It will be seen that all the explanations of suspension stability support Gruber's theory, that the cause of agglutination is increased adhesiveness of the cell surfaces, though the modern school sees in the increased viscosity only one of the causes of the suspension stability, and considers

the diminution of the electrical burden caused by the adsorption changes an equally important factor.

It appears probable that the suspension stability is a complex phenomenon, produced by several factors, which cannot be explained by one theory. Regardless of which theory will be finally accepted, the clinician is mostly interested in one fact, which has been brought out by this extensive research work, that is, that variations in the relative protein composition of the blood are responsible for the changes in the sedimentation speed, and that the latter is directly proportional to the globulin level and indirectly to the albumin content of the blood. The quantitative increase in fibrinogen in the blood has long attracted the attention of the clinicians and it is of interest to note that all those conditions, in which the fibrinogen level is higher than normal, usually show an increased sinking speed. Foster and Whipple have shown that acute inflammations are invariably associated with high fibrin and fibrinogen values and, on the other hand, are characterized by an increased speed of sedimentation, which is in proportion to the extent and grade of inflammation (Fahraeus, Linzenmeier), as, for instance, in pneumonia and diffuse peritonitis, which usually show the highest sinking velocities.

It is more than a coincidence that in pregnancy the fibrinogen fraction is high and at the same time the sinking velocity is so markedly increased, and that Fahraeus at first recommended this test as a test for pregnancy. And Durand has observed that there is in pulmonary tuberculosis sometimes a considerable increase in globulin and a reduction of the albumin fraction. At the same time, all writers who have used the sedimentation test in tuberculosis patients have noted a markedly increased sinking velocity in all active cases. Since the increase in fibrinogen can be attributed to the breaking down of tissue (Frisch) the sedimentation test can be considered as a measure of the amount of tissue destruction.

It is highly probable that the sedimentation speed can be influenced by other factors aside from changes in the relative protein composition of the plasma. Bonninger and Hermann point out that the number and the size of the red corpuscles is an important factor, and they explain the higher values of sinking speed found in women by the smaller size of their erythrocytes and the increased sinking speed found in anemias by the reduced number of red cells. Plaut ascribes the retarded sedimentation in polycythemia to the increased friction between the increased number

of cells. Bloch and Elsner finally claim that Stoke's formula holds good in sedimentation and that macrocytes sink more rapidly than microcytes on account of their greater diameter.

TECHNIQUE

Various methods have been employed and many modifications have been advocated, but they all are more or less alike, and differ only in the size of the tubes, the concentration of the sodium-citrate solution and the amount of blood employed. They all can be classified according to the principle of measuring either first, the sedimentation time (method of Linzenmeier) or, second, the sedimentation speed (technique of Westergren), the former favored mostly in surgery and obstetrics, the latter in internal medicine. Of the American writers, Levinson has employed Fahraeus's original technique. Friedlander has used Linzenmeier's technique, which has the obvious disadvantage that one has to be on the look-out for the maximum of sedimentation all the time, which is hardly possible in an institution, where the sedimentation test is used as a routine examination for all patients. With Westergren's technique the time when the readings are taken depends on the time when the blood is withdrawn only, and not on the plasma of the patient, and for this reason we have adopted Westergren's method.

The proportion of sodium citrate to the amount of blood of 1:4 has been generally accepted, whereas the concentration of sodium citrate employed by various investigators ranges from 3 to 5 per cent. As we have to deal with comparative values, the concentration within these limits is probably of no importance, provided the same concentration is used in all tests (Hasselhorst). We have employed a 3.8 per cent concentration, which according to Westergren is the isotonic solution, because Puxeder claims that the best and quickest results are obtained with a solution of about 3 per cent. Opinion is divided as to whether the internal diameter of the tubes has an influence on the speed of sedimentation or not. Westergren believes that the diameter is more or less immaterial, but admits that a tendency to more rapid sedimentation can be observed in narrower tubes, and Hasselhorst claims that differences of 1 to 3 mm. are without any importance. Conversely, Horvat and others state that the test of the same blood in narrower tubes yields higher values than in wider tubes. We have made many tests in tubes of different sizes to decide this question, and our observations have con-

vinced us that both statements are correct,—Horvat's as regards the absolute figures, which are decidedly higher in tubes with a smaller calibre, and Westergren's regarding the relative values calculated in percentage of the whole column.

In order to exclude possible mistakes caused by the unavoidable variations in the diameter of the tubes which are on the market, Westergren has abandoned the principle of the constant quantity of blood for that of the constant height; and properly so, because the diameter is more or less immaterial and only the height of the column is important. It is however evident that the same amount of blood should always be used, and we doubt very much whether tests which differ in 0.5 to 1 cc. of amount of blood, employed with differences of from 2 to 5 millions of erythrocytes, can be compared. The ideal method would be constant height and constant quantity of the blood; and I have therefore used indiscriminately tubes of 2/8 to 3/16 inch in diameter, but express the result not in absolute figures but bring them into relation to the height of the whole column by calculating the height of the clear column in percentage of the whole suspension column. The test is thus made free from mistakes arising from the irregular and varying diameter of the tubes, the same amount can be employed in all tests, and for statistics the percentage will facilitate comparisons which are at present impossible, due to the confusing diversity of methods. For instance, 2 per cent corresponds to 4 mm. Westergren's and 2.4 mm. Hasselhorst's, who employs a constant column of 12 cm.

We have made many tests with different quantities of blood of the same patient emptied at the same time into sedimentation tubes of different diameters, and we have convinced ourselves that the only factor which really matters is the height of the whole column, and that the percentage is a true expression of the sinking velocity. One example (table 1) will show how exactly the heights of the clear columns tally with each other as expressed in the percentage which they bear to the heights of their whole respective columns.

TABLE 1

Case no. 68

QUANTITY	COLUMN	1 HOUR		2 HOURS		6 HOURS		24 HOURS	
cc.	*mm.*	*mm.*	*per cent*	*mm.*	*per cent*	*mm.*	*per cent*	*mm.*	*per cent*
2.5	119	27	23	41	34	60	50	65	54
1.5	85	20	23	30	35	43	50	46	54
1	75	18	24	26	34	37	50	41	54.5

Sometimes, however, differences of from 3 to 5 per cent are found, especially if the height of the column is more than 20 cm. or less than 10 cm., but these differences are negligible if the height of the column ranges between these limits.

The technique: Into a sterilized, dry, 2 cc. syringe 0.4 cc. of a 3.8 per cent sodium-citrate solution is drawn, the cubital vein is punctured after a short stagnation and blood up to the 2 cc. mark is withdrawn. The solution is thoroughly mixed by slowly inverting the syringe several times and is emptied into a clear and dry sedimentation tube. The tubes are placed in a vertical position in a test-tube rack at room temperature, and the readings are made after 1, 2, 6 and 24 hours. We added the reading after 6 hours because the sedimentation in very advanced and active cases is sometimes practically completed in 6 hours, and because this additional reading enables us to estimate the sedimentation time as well as the sedimentation speed.

METHOD AND RESULTS

After some experience with the sedimentation test we introduced it as a routine examination, to be made in all patients on admission and to be repeated at regular intervals, into the Sanatorium of the Jewish Consumptive Relief Association of California at Duarte. The literature on this subject is so extensive that we had no intention of publishing our observations. The purpose of our investigations was to determine whether and how the sinking velocity of the blood changes in patients who are treated by artificial pneumothorax. It suggested itself that a treatment, which stops a destructive process and brings about increased fibrosis in the compressed parts, must necessarily influence the sedimentation speed. It was to be expected that in unilateral cases the sinking velocity must come down to normal values, if the parts where the destructive process is located are well compressed. On the other hand, no change or an acceleration in the sinking velocity would signify that the pneumothorax treatment is not successful, either because the involved parts are not sufficiently compressed or because in bilateral cases the better side, subjected to the increased strain, is flaring up, and is or becomes the seat of a destructive process, which causes the increased rapidity of the sedimentation. In short, we wanted to investigate whether the sedimentation test could be useful as a method to determine whether the artificial-pneumothorax treatment is successful and whether and how long it should be kept up. The number of cases observed since

October, 1923, is too small to draw any definite conclusions; still our observations indicate that the sedimentation speed decreases and approaches normal values if the other clinical symptoms show that the treatment is successful and that the sinking velocity does not change or is accelerated, if a good compression cannot be obtained, or if in bilateral cases the other side contraindicates the continuance of the artificial pneumothorax. As a by-product of our investigations we had the opportunity to make observations regarding the sedimentation test in pulmonary tuberculosis in general, which we want to report shortly because they differ in several regards from those of other observers.

On the whole, we can confirm the findings of Levinson, Westergren, Dreyfuss, Hecht, Katz and other observers, that there is a marked difference in the sinking velocity between the early, moderately advanced, and advanced cases, both and especially in the values after 1 and 2 hours. But we want to add that many exceptions to this rule are found, especially by repeated tests, and that the results of the sedimentation test have to be taken into consideration in conjunction with the other clinical symptoms and cannot be the basis for a classification by itself. We cannot expect too much from any method of examination, and anybody who would rely exclusively on suspension stability is bound to have disappointments. We have to bear in mind that tuberculosis in its chronic course is characterized by a lability of all symptoms. All immunity tests have proved, more or less, failures in pulmonary tuberculosis, because the content of the blood in antibodies, for instance in complement-fixation antibodies, changes from day to day and from hour to hour, as Much has pointed out; and the same changeability can be observed in the sedimentation test too. Several times in repeated tests we were surprised by an unexpected increase or decrease in the sinking velocity, for which we sometimes failed to detect any reason. The conditions in acute diseases are, after all, entirely different from those prevailing in tuberculosis, and the suspension stability is, therefore, more reliable and of greater value in acute conditions, with their sudden changes in the relative protein composition of the plasma, which disappear as promptly and quickly as they appeared as soon as the inflammation has subsided and the tissue destruction has ceased. In tuberculosis, however, in which the degree of destruction and repair, and consequently the amount of globulins in the blood, changes continuously, fluctuations in the sinking velocity must be expected, for which we sometimes cannot find an explantaion with our clinical methods, and

there is no doubt in our minds that there are variations of the suspension stability, dependent on the temperature and other constitutional symptoms of the patients. Even in healthy persons, variations up to 100 per cent were observed by Opitz and Frei, and the fluctuations in tuberculosis patients are, for obvious reasons, more marked and more frequent.

According to Levinson, the sinking values in healthy men average 0.33 cm. and in healthy women 0.74 cm. per hour, and any values above 0.9 cm. for men and 1.2 cm. per hour for women must be regarded as pathological. We have found similar values, and consider 2.5 per cent in healthy men and 4 per cent in healthy women as normal for the first hour and 40 per cent as normal end values after 24 hours. A sedimentation speed for the first hour above 5 per cent for men and 7 per cent for women is indicative of pulmonary tuberculosis if other organic diseases can be excluded. The increase in the sinking velocity is in proportion to the extent of the anatomic involvement of the lungs and to the activity of the process, and is therefore more marked in moderately advanced cases than in incipient, and still higher in far advanced cases. It is higher in febrile patients than in afebrile patients with a corresponding lung involvement.

Our values for incipient, and moderately and far advanced cases, especially in the latter group, are higher than those found by Levinson; the differences are marked, though considerable deviations in both directions from this average are occasionally observed. The average percentage for the first hour is, for incipient cases, around 10 per cent; for moderately advanced, about 20 per cent; and for far advanced, about 35 per cent. The final values, too, are higher in the group of far advanced cases, lower in moderately, and lowest in incipient cases (60, 50 and 45 per cent, respectively). In each group the cases with a tendency to fibrosis show a lower and the ulcerative type the highest average. The highest sedimentation percentage was found in cavity cases with fever, in hemorrhage cases, and in pulmonary tuberculosis associated with secondary tuberculosis in other organs (Levinson), with the exception of tuberculosis of the throat, which does not seem to increase the sedimentation speed, and in spontaneous pneumothorax. We had the occasion to observe 6 cases of spontaneous pneumothorax and found a sedimentation average of 50 per cent for the first hours with final readings of 65 per cent. In one case with effusion the final value was as high as 74 per cent, the highest we have ever observed.

Sedimentation tests repeated at regular intervals, in many patients,

showed us that there is a satisfactory, though not complete, parallelism between the course of the disease and the changes in the sedimentation speed. Increased activity or a spreading of the diseased area is very often coincident with higher sedimentation values, whereas in most cases the sinking velocity decreases gradually and steadily the more all constitutional and physical symptoms subside and the more general condition improves. To illustrate to what extent the sinking velocity may change in patients who show a marked improvement in their general and lung conditions, a few cases are reported (table 2).

TABLE 2

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 43				
			per cent	*per cent*	*per cent*	*per cent*	
10–27–23	28	Male	20	42	58	64	Far advanced, positive sputum. Afebrile. Was. neg. Plus 3 pounds. Small cavities in both upper lobes
12–25–23			25	41	54	60	Plus 8½ pounds
2–20–24			13	37	51	59	Plus 2½ pounds, condition much improved
4–26–24			13	29	46	50	Plus 1¼ pounds, less moisture. Apparently quiescent
			Case no. 63				
12–12–23	43	Male	41	52	56	57	Far advanced with small cavities. Positive. Plus 10 pounds in two weeks. Afebrile
3–18–24			23	36	55	59	Plus 7 pounds. Cough and expectoration decreased
4–27–24			9	19	41	42	Plus 2¾ pounds, much improved, sputum neg.
			Case no. 126				
1–12–24	26	Female	36	50	53	54	Far advanced, double-sided. Retraction and fibrosis left side. Afebrile, positive
2–12–24			27	44	59	62	Plus 3½ pounds
3– 9–24			21	32	47	53	Plus 1 pound, improving
4–28–24			14	29	46	52	Cough and expectoration greatly diminished. Condition much improved

TABLE 2—*Continued*

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 127				
			per cent	*per cent*	*per cent*	*per cent*	
1–17–24	24	Female	17	25	52	54	Far advanced, right-sided case. Several slight hemorrhages. Cavity right upper lobe. Pneumothorax tried unsuccessfully. Positive. Afebrile.
2–23–24			12	23	42	53	Plus 1 pound
4–28–24			3.5	10	33	47	Less moisture, cough and expectoration subsiding

On the other hand, the sedimentation speed usually is not changed or increased in unimproved or progressive cases. After a severe hemorrhage or an acute complication we often find a sudden, mostly temporary increase in the sinking velocity as the following examples show (table 3):

TABLE 3

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 11				
			mm.	*mm.*	*mm.*	*mm.*	
10–23–23	24	Female	147	151	161	163	Far advanced, double-sided case. Cavity right upper lobe. Febrile. Positive sputum. Plus 2 pounds
			per cent	*per cent*	*per cent*	*per cent*	
12–25–24			37	52	62	66	Subfebrile
2–12–24			42	56	58	59	Weight stationary. Temperature normal
4–20–24			53	59	66	66	Severe hemorrhage, April 19, lasting 3 days. Subfebrile
			Case no. 76				
12–30–23	27	Male	32	48	61	64	Far advanced, left-sided case with cavity formation. Hemorrhage case. Positive sputum, subfebrile
3–29–24			50	52	66	67	After severe hemorrhage and tonsillitis
4–28–24			12	24	41	53	Temperature normal, gain in weight

In trying to correlate the relationship between the course of the disease and the changes in the suspension stability we found, in 100 tests, a parallelism 78 times, as the sedimentation speed was decreased in 63 cases, the condition of which had improved, and increased in 15 progressive cases, whereas a discrepancy was observed 22 times, 16 patients who had improved, showing unchanged or higher sedimentation values, while 6 progressive cases gave slightly better sedimentation results.

Since the increased sinking velocity is generally regarded as a sign of increased tissue destruction, it was most interesting to investigate the relationship between changes in weight and variations of the sedimentation speed, and we found that in the majority of cases gain in weight is accompanied by a decrease, loss in weight by an increase in the sinking velocity. In 100 tests, gain in weight went hand in hand 62 times with a decreased sedimentation speed, and loss in weight 15 times with an increased sedimentation speed. The opposite observation was made in 23 cases, gain in weight together with an increased sedimentation being registered in 18 patients and loss in weight with a decreased sedimentation speed in 5 patients. It is not at all surprising that the parallelism is not complete, as weight can be put on in excess of the degree of wasting and, on the other hand, loss in weight can be caused by nonspecific conditions of the intestinal tract.

The changes, which we observe in subsequent tests, are often noticeable in all values; sometimes, however, certain readings only show an increase or decrease, so that the sedimentation curve becomes entirely different in type. Our observations lead us to believe that the prognostic value of the sedimentation curve is as high as the sedimentation speed, if not higher, and that the prognosis seems to be better the more the sedimentation curve approaches the curve of normal sedimentation. In healthy persons the settling of the erythrocytes is slow during the first hour, is somewhat more rapid during the next five hours and slows down again from the sixth up to the twenty-fourth hour. If we mark down the time of standing expressed in hours on the abscissae and the sedimentation percentage on the ordinates, the normal sedimentation curve is represented by an ascending almost straight line, which has a slight elevation at the 6-hour mark and runs obliquely toward the 40 per cent line. We have been able to distinguish three types of sedimentation curves, each of which has a different prognostic

meaning. The first type found in fibrotic and incipient cases allows the best prognosis. It resembles the normal sedimentation curve, with the only difference that it runs at a higher level, all values being uniformly increased (see curve 1).

The second type is characterized by a marked acceleration of the sedimentation during the second hour, whereas the first-hour values are about or slightly above normal. This sedimentation curve is represented by a steeply ascending limb, corresponding to the second hour, after which a straight line runs almost horizontally toward the 24-hour mark. The prognosis in cases in which this sedimentation type is found is rather favorable. Very often we found, in subsequent tests, all values, but especially the 2nd and 6-hour values, much decreased, so that this type frequently turns into type 1, as the patient continues to improve (curve 2).

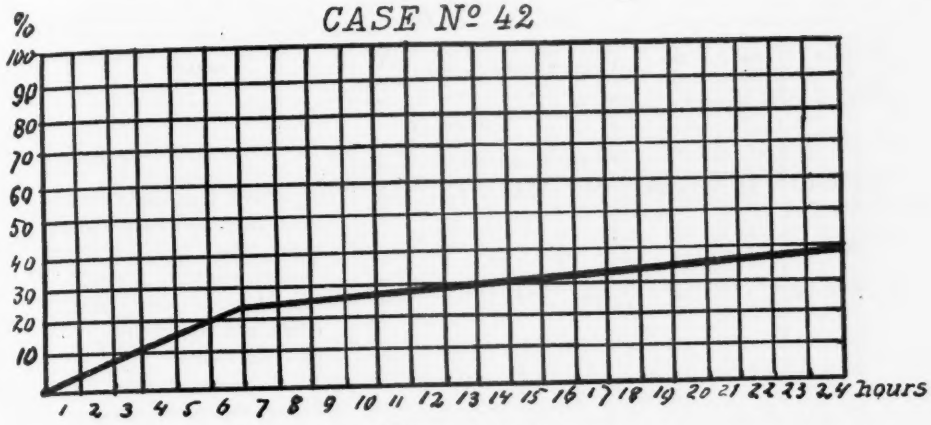
The third curve is distinguished by an almost vertical ascending limb during the first hour and an almost horizontal limb with a sharp angle at the first-hour point. The sedimentation is practically completed within the first hour. The prognosis in these cases is decidedly unfavorable. We have observed a number of patients with this characteristic sedimentation curve, and can say that the majority of these patients died within a few months and that the prognosis in all these cases is as unfavorable as possible.

THE SEDIMENTATION RATE IN ARTIFICIAL PNEUMOTHORAX

We have had 11 cases of artificial pneumothorax under observation, in which we controlled this treatment by regularly repeated sedimentation tests, and have had the experience that this simple test is a valuable and reliable means to determine the effect of the compression. In all observed cases the variations in the sedimentation speed corresponded to the clinical symptoms and physical findings, by which we usually determine whether the treatment is successful or not, and in three cases the increase in the sinking velocity, together with other signs of spreading of the diseased area or of insufficient compression, induced us to discontinue the artificial-pneumothorax treatment. In the remaining 8 patients, who improved considerably, the sedimentation speed decreased steadily, as is demonstrated by the following table 4.

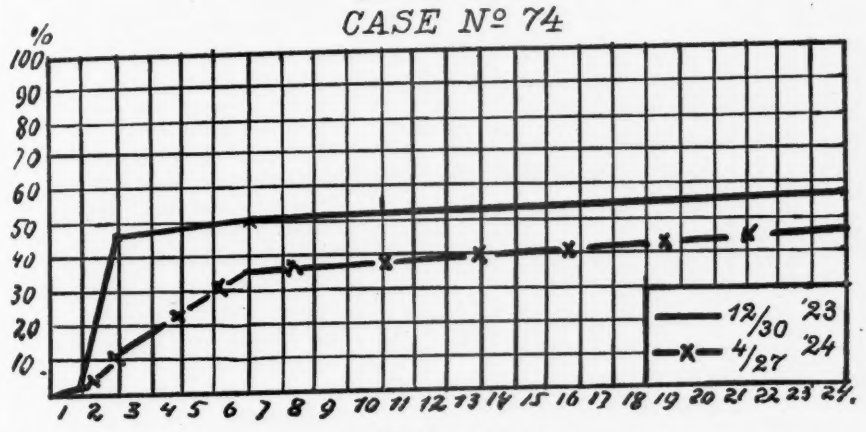
CURVE 1

CASE Nº 42



CURVE 2

CASE Nº 74



CURVE 3

CASE Nº 50

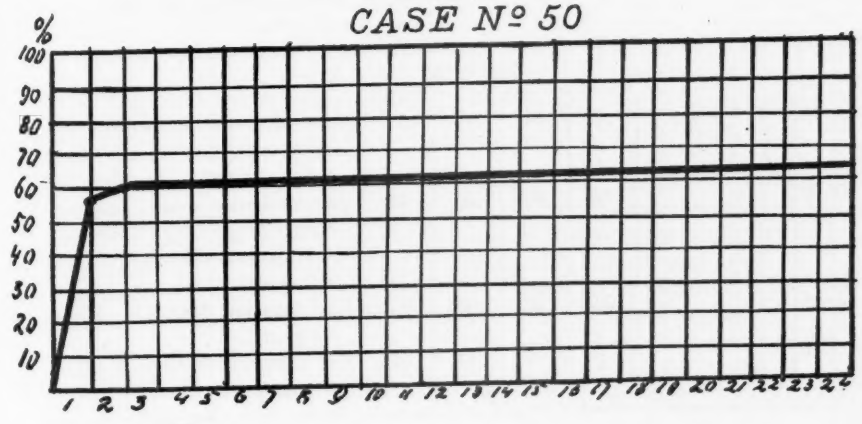


TABLE 4

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 21				
			per cent	*per cent*	*per cent*	*per cent*	
10–24–23	32	Female	51	58	62	65	Very active, progressive double-sided case with cavity in left upper lobe. Loss in weight. Sputum positive. Febrile
2–20–24			48	59	63	64	Minus 3½ pounds, temp. normal. Right side clearing up
3–18–24			28	50	60	71	Weight stationary
3–27–24			57	65	69	71	Artificial pneumothorax March 21; left side partly compressed
4– 6–24			27	47	66	70	Last inflation Mar. 27. Plus 3 pounds
4–22–24			23	41	62	65	Last compression April 17
5–11–24			17	39	55	64	Last compression May 8. Plus 1 pound
			Case no. 38				
10–27–23	21	Male	43	55	59	59	Involvement of whole left side: positive sputum, afebrile, minus 2 pounds
12–14–23			18	30	41	42	Pneumothorax since Nov. 23. Good compression. Small effusion. Minus 3 pounds
2–20–24			26	51	58	63	Last compression Feb. 15. Plus 3 pounds
3–25–24			23	45	54	57	Last compression Mar. 19. Plus 1½ pounds
4–22–24			11	25	48	55	Last compression April 6
5–11–24			15	35	53	55	Last compression April 25. Plus 1 pound
			Case no. 80				
1–24–24	31	Male	18	34	53	59	Far advanced left-sided case with softening in left upper lobe. Afebrile. Positive
2–20–24			37	40	40	41	Pneumothorax since Jan. 23. Left side partially compressed. Last inflation Feb. 15. Minus 2½ pounds
3–25–24			24	46	60	62	Last inflation Mar. 21. Minus 2¾ pounds
4–22–24			9	24	44	55	Last compression April 17. Plus 1 pound

TABLE 4—*Continued*

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 103				
			per cent	*per cent*	*per cent*	*per cent*	
11– 2–23	17	Female	29	43	58	60	Far advanced. Dense infiltration of the whole left lung. Small hemorrhagic effusion. Subfebrile. Positive
12–24–23			19	53	56	59	Temp. occasionally subfebrile
2–11–24			30	43	57	61	Artificial pneumothorax since Jan. 27. Last compression Feb. 8. Minus 2 pounds, temp. normal
2–22–24			17	34	54	59	Last compression Feb. 15. Plus 2 pounds
3–18–24			7	24	52	59	Last compression Mar. 14
4–23–24			7	29	53	61	Last inflation April 17. Plus 2 pounds
5–21–24			10	27	48	58	Last compression May 13. Plus 1 pound
			Case no. 125				
1–12–24	27	Female	24	35	54	62	Far advanced left-sided case. Good compression of left side: pneumothorax since Aug. 18, 1922
2–12–24			20	49	58	61	Last compression Feb. 9. Plus 3¼ pounds. During menstruation
2–22–24			15	29	50	55	Last inflation Feb. 20
3–19–24			7	15	49	54	Plus 5½ pounds. Last compression Mar. 12
4–22–24			13	27	44	54	Last compression April 9. Last menstruation April 3. Plus 3½ pounds
			Case no. 13				
			mm.	*mm.*	*mm.*	*mm.*	
10–23–23	23	Female	136	145	151	163	Far advanced, very active, left-sided case. Caseous pneumonia of lower lobe. Febrile
			per cent	*per cent*	*per cent*	*per cent*	
12–14–24			6	29	58	61	Pneumothorax since Nov. 7. Good compression. Plus 4 pounds. Temp. normal
2–12–24			39	54	61	63	Last compression Feb. 1. Minus 1 pound
2–22–24			42	57	65	65	Weight stationary
3–19–24			33	48	57	63	Last compression Mar. 14. Minus 2 pounds
4– 6–24			16	31	51	61	Last pneumothorax Mar. 27
4–22–24			13	26	43	55	Last inflation Apr. 11
5–13–24			7	21	40	51	Last compression May 8

TABLE 4—*Continued*

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			Case no. 4				
			mm.	*mm.*	*mm.*	*mm.*	
10–20–23	20	Male	74	94	96	98	Double-sided case, involvement of whole left side with cavity. Small softening zone below clavicle in right upper lobe. Minus 10 pounds. Positive. Afebrile
			per cent	*per cent*	*per cent*	*per cent*	
12– 4–23			28	39	52	62	Pneumothorax since Nov. 13. Last inflation Nov. 28. Left lung well compressed. Moderate amount of effusion
2–20–24			46	53	53	54	Last compression Feb. 15. Minus 1 pound
3–25–24			49	63	69	72	Last pneumothorax Mar. 13. Plus ½ pound
4–22–24			38	54	63	64	Last compression April 17
5–13–24			33	47	53	54	Plus 1 pound. Last compression May 8
			Case no. 143				
3–10–24	30	Male	11	14	32	47	Moderately advanced. Artificial pneumothorax since 4 months. Good compression right side. Negative. Afebrile
3–25–24			3	16	53	56	Plus 2 pounds. Last pneumothorax Mar. 21
4–22–24			3	8	35	45	Last compression April 17. Plus 2 pounds

Table 4 illustrates the parallelism between the changes in the sinking velocity and the effect of the pneumothorax treatment. It will be noted, however, that the steady decrease is occasionally broken by a marked increase, usually in the beginning of the treatment. We are of the opinion that this temporary increase in the sedimentation speed can be attributed to the anatomic changes which take place in the compressed parts of the lungs. In the beginning of treatment by artificial pneumothorax, we occasionally observe an increased amount of sputum and a rise in temperature, and it appears highly probable that the augmented destruction of tissue, due to inflammatory demarcation in the compressed areas, leads to a temporary increase in the sinking

velocity, which can be easily differentiated from the progressive and permanent increase in the speed of sedimentation by careful examinations of the patient and by repeated tests. Case 4 is in this regard very interesting. The young man was not an ideal case for pneumothorax, having an area of softening, with bronchovesicular breathing and mucous râles below the right clavicle. Nevertheless, artificial pneumothorax was induced on the left side, and the right side was very closely watched. For nearly five months he showed high sedimentation values, but as there was no evidence of a flare-up in the right side we decided to continue the treatment. The last sedimentation tests yielded decidedly better results, and we are hoping that we will be able to keep up the pneumothorax in this patient. Incidentally, we want to point out that he has a serious effusion on the left side, which condition is always associated with higher sedimentation values.

The tests were purposely repeated at different times between the inflations in order to find out whether the degree of compression has an influence on the sedimentation speed, and to investigate whether the test can be used as a means to determine the optimum of pressure and intervals between the inflations. Our observations seem to indicate that the lowest values are obtained from 4 to 5 days after the inflation and that higher values might be found from one week to 10 days after the refill. It is therefore advisable to make the tests regularly on a certain day after the inflation.

In three cases the sedimentation test in conjunction with the clinical findings induced us to discontinue the artificial pneumothorax (tables 5, 6 and 7).

TABLE 5

Case no. 131

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			per cent	*per cent*	*per cent*	*per cent*	
1–24–25	23	Female	42	53	57	60	Far advanced, left-sided, with slight involvement of right side. Positive. Febrile
2–28–24			44	55	59	62	Artificial pneumothorax induced Jan. 20. Last compression Feb. 20. Right side flaring up. Temp. higher. Pneumothorax discontinued

In this patient (table 5) the temperature rose to 101° after the third inflation and remained high for nearly three weeks. On examination

we found a marked spreading of the diseased area at the base of the right upper lobe, which contraindicated the continuance of the pneumothorax. The patient is afebrile at present and shows a remarkable improvement.

TABLE 6

Case no. 68

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			per cent	*per cent*	*per cent*	*per cent*	
12–24–23	27	Male	6	16	48	56	Far advanced, left-sided case with cavity. Subfebrile. Positive sputum
2– 3–24			26	37	57	64	
2–20–24			8	44	52	52	Pneumothorax since Feb. 5. Last inflation Feb. 19. Temp. normal
3–22–24			23	34	50	55	Temp. normal. Minus 3 pounds. Last inflations Mar. 14 and 21

After a temporary increase in the sedimentation speed (table 6) we observed a considerable decrease; however, one month later the sedimentation was markedly accelerated again. The patient had lost in weight, was short of breath, wherefore discontinuation of the pneumothorax was considered. Shortly afterward, the patient left the institution.

TABLE 7

Case no. 106

DATE	AGE	SEX	AFTER 1 HOUR	AFTER 2 HOURS	AFTER 6 HOURS	AFTER 24 HOURS	REMARKS
			per cent	*per cent*	*per cent*	*per cent*	
11–15–23	23	Female	50	66	74	74	Far advanced double-sided case. Spontaneous pneumothorax with serous effusion on left side. Febrile. Positive. Much wasting
2–11–24			56	65	71	72	Aspiration of 500 cc. of serum replaced by air. Last inflation Feb. 8
2–22–24			63	69	72	72	Last compression Feb. 15. Febrile
3–18–24			61	69	74	75	Temp. febrile always. Loss of weight. Pneumothorax was discontinued. Last inflation Mar. 14
4–27–24			56	65	70	73	

Progressive double-sided case (table 7). Pneumothorax, in replacement of serous effusion, was kept up for 5 weeks. Higher temperatures, increased moisture on the right side and increased sedimentation values were sufficient contraindications against further compressions. Patient died after an acute spontaneous pneumothorax 8 weeks later.

CONCLUSIONS

The sedimentation test is very valuable and useful in patients who are being treated by artificial pneumothorax. In conjunction with the methods of clinical examinations it helps us to determine the effect of the compression and is a simple means of controlling the influence of the pneumothorax on the better side. In the beginning of the treatment, we occasionally can observe a temporary increase in the sedimentation speed, which is without significance.

With regard to sedimentation in pulmonary tuberculosis we can, on the whole, confirm the findings of Westergren, Katz, Dreyfuss and Hecht, Levinson and others.

The sedimentation test is of diagnostic value in doubtful cases of pulmonary tuberculosis. The prognostic value is not as great in pulmonary tuberculosis as in acute conditions, on account of changes which are sometimes observed in its chronic course.

There is a marked difference in the sinking velocity between early, moderately advanced and far advanced cases, and between the fibrotic and ulcerative types of pulmonary tuberculosis.

In view of the confusing number of methods a standardization of the technique is highly desirable.

The sedimentation speed can be expressed by the percentage which the height of the clear plasma column bears to the height of the whole column, regardless of the calibre of the tubes, if the diameter is between 3 and 5 mm., and of the height of the column, which may range from 10 to 20 cm.

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OBSERVATIONS ON PARTIAL ARTIFICIAL PNEUMOTHORAX IN EARLY PULMONARY TUBERCULOSIS

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I do not intend to describe the usual procedure in artificial pneumothorax, but to speak of the results of my observations for the past four years, during which I have been giving artificial pneumothorax in over 100 cases, and to advocate partial collapse in preference to total collapse, not only in advanced or hemorrhagic cases, but also in more early stages. My experience and that of others have convinced me that periodic partial pneumothorax is an efficient treatment for certain types of tuberculosis. In fact, for the past two and a half years I have been using this treatment in many more patients than formerly, often disregarding the amount of involvement.

Like many others, I originally employed artificial pneumothorax solely as a method of arresting hemorrhages. Gradually I began to use it as a method of treatment in far-advanced cases, regardless of whether there was unilateral or bilateral involvement. In bilateral cases I selected the most advanced side for collapse and the results in some were gratifying.

Complications such as have been described by those who are doing artificial pneumothorax, which cause the treatment to be ineffective or to be stopped, are much less frequently met with in early stages of the disease. Firm pleuritic adhesions, the most common interference with the procedure, are not by any means so great.

If one is of the opinion that a case ought to have an artificial pneumothorax, it should be administered, even though the X-ray shows adhesions, and often one will find that by so doing one will meet with success.

We now know that the danger incident to the administration of air is trifling and practically negligible. Exactly the same measure of safety is involved in the effecting of a series of partial collapses. To give a patient a partial pneumothorax, and continue the treatment every week for a few months at least, is wise and beneficial.

The early use of partial pneumothorax is particularly indicated for the

early cases which in spite of the most careful treatment show little improvement, and for those that respond to complete rest, yet develop clinical symptoms and physical signs with the least exertion.

My experience with partial collapse has led me to the conclusion that partial pneumothorax is efficient in securing fibrosis around the diseased area. Such fibrosis tends to be permanent under the partial collapse, since there is no distention or tearing as in complete collapse. Barlow and Kramer (1) in their recent work came to the same conclusion.

A partially collapsed lung shows a decreased tendency toward adhesions and it is less in danger of the development of spontaneous pneumothorax. In the administration of partial pneumothorax we collapse only the diseased tissue, allowing healthy tissue to function. There is also eliminated the danger of the displacement of the mediastinum. A partial pneumothorax may be used alternately in both lungs.

I have attempted to induce artificial pneumothorax in 102 cases of pulmonary tuberculosis. In 26 advanced cases it was impossible to produce a pneumothorax on account of adhesions. In 12 moderately advanced cases no improvement was noticed after several injections. In another case the pleura was so cartilaginous that it was impossible to penetrate it, and the X-ray showed a greatly thickened pleura. Twenty-nine of the 102 cases had slight unilateral involvement and 5 of these showed adhesions which did not prove obstacles to treatment. Thirty-four were moderately advanced cases. The oldest patient was 68, the youngest 10 years. In only one of my cases did a complication arise; that is, the development of fluid after the second injection. I then aspirated and replaced the fluid by air, and continued treatment.

While numerous other observers have reported such complications as pleural shock, embolism, spontaneous pneumothorax, empyema, etc., I have been more fortunate in my cases in which pneumothorax was done. The probable explanation may be due to the fact that pneumothorax was done early in the disease.

The method of procedure is as follows: Morphine sulphate, gr. $\frac{1}{4}$, and atropine sulphate, gr. $\frac{1}{150}$, are given 15 minutes before the operation. The skin is then washed with alcohol and anesthetized with novocain and adrenalin. I use the puncture method in preference to the skin incision. The first injection is given with the patient lying in bed at home. An associate records the pulse, watches the manometer and looks out for unusual symptoms. When the manometer shows the proper reading 50 cc. of air is given. However, irrespective of the manometer

reading, if the patient complains of pressure or discomfort, treatment is discontinued. The subsequent treatments are given once a week at the office, if the condition of the patient permits. The advantage of office treatments is that we may have fluoroscopic control. It is of advantage to perform the operation with the patient sitting in a chair, his leg sastride, his back toward me, his face toward the back of the chair, and his chin resting upon his folded arms on the top of the chair. This position has a tendency to spread the intercostal spaces, and thus allow freer access.

A needle I use is one with the two-way stop-cock described by Rosenblatt (2). The advantage of this needle is that anesthesia can be produced and the air introduced without removing the needle. An interesting device which I have found to be of considerable value is that I have placed upon the needles I use, sliding clamps similar to the devices used to insure the safety of stick-pins. These clamps can be made to hold at any point on the length of the needle desired, and thus they allow the needle to penetrate at neither more nor less than the desired depth. Thus, when the needle has penetrated a sufficient depth into the pleural cavity, the clamp is adjusted, and no further accidental penetration is possible.

Most workers do not state definitely how long the treatment should be kept up. In my practice I have discontinued treatment after six or seven months. In three cases it became necessary to reëstablish the pneumothorax. None of the cases was in a sanatorium during the entire course of treatment. Of the 29 early cases of tuberculosis, 12 are at work and the rest are improved. Only three of the moderately advanced cases are at work.

CONCLUSIONS

1. Partial artificial pneumothorax is a very valuable remedy in the treatment of pulmonary tuberculosis.

2. Complications incident to the pneumothorax are lessened when treatment is begun early in the disease.

3. The length of the treatment necessary to obtain improvement is lessened by beginning early.

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ON ANTICIPATORY DETUBERCULIZATION

A PRACTICAL PROCEDURE

SIR ROBERT PHILIP[1]

When the tubercle bacillus as the essential cause of tuberculosis was authoritatively announced, it took a long time until the practical bearings of the fact were fully realized. Yet the determination of the infective nature of tuberculosis implied the scientific principles on which prevention and treatment must be based. Admission of its infective character implied responsibility to apply to tuberculosis the general principles of prevention and treatment which had been applied successfully to other infective diseases, with such modifications and additions as the special characters and natural history of tuberculosis required.

One of the most significant lines which recognition of its infective nature and endemic distribution enforced was that tuberculosis *must be searched for*. It became evident that it was a mistake, for the most part, to wait until patients presented themselves for treatment. This had been the cause of ill success in the past. The great majority sought treatment after the disease had run riot within the patient's system. The case the physician was asked to see for the first time was commonly one, not of infection merely, but of gross disturbance, and even disorganization of viscera, following successful, prolonged invasion. Similarly, the case the surgeon was asked to see was frequently one of grave crippling through gross involvement of bone and joints, with disintegration of tissue elements and corresponding functional derangement.

It became apparent, scientifically and economically, that, if we were to make serious progress, there must be instituted a *systematic hunt* for tuberculosis in its earliest manifestations. Cases must be detected before the disease had been allowed to make headway. The advanced case of tuberculous disease, whether in viscera or in skeleton, was really the expression of ignorance and neglect. It was demonstrated that cases

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were remediable in proportion to earliness of detection, and the fact had both medical and communal interest.

The recognition of the infective nature of tuberculosis and the supreme significance of early detection formed the *motif* for the institution of the tuberculosis dispensary. The purposes and possibilities of that instrument in the antituberculosis armamentarium need not be discussed for the moment. It is sufficient to recall that through the varied activities of the tuberculosis dispensary, when efficiently organized, tuberculosis is discovered, time after time, at the earliest moment through the examination of "contacts,"—cases which in former times would never have come under consideration at that stage. Thereby it has been possible to enforce measures in respect both of the individual and of his environment, which have proved preventively of incalculable value to households and to the community.

The pursuance of such measures and the application of bacteriological principles—notably in the diagnostic use of tuberculin—in association with other pathological and epidemiological studies, have led to the recognition of two great facts of far-reaching importance with regard to tuberculosis. Those are (1) *that tuberculous infection is more or less universal throughout civilized populations* and (2) *that infection takes place during childhood in the vast majority of instances.*

With those fundamental facts may be associated the increasing acceptance of the view, based on the *phenomenon of Koch* and on continued observation of the natural history of the disease in the same individual from childhood throughout life, that for the most part the emergence of tuberculous disease in later life, in whatever part of the body the emergence occurs, is to be referred *ultimately* to initial infection in childhood.

The immediate purpose of the present paper is to ask whether, alike from the medical and from the economic point of view, sufficient value has been attached to the *consequences of those far-reaching facts.* The answer seems obviously in the negative. What serious attempt has been made, on any large scale, to apply the practical lessons that naturally follow therefrom?

During a number of years it has been my endeavor to introduce, and it has been my custom to inculcate in students, the practice of what for convenience I have termed *Anticipatory Detuberculization.* The procedure is based on the recognition of the principles to which allusion has just been made.

If the great majority of the ordinary population acquire tuberculous

infection in the fashion indicated, that is, become tuberculized, and if, as will be admitted, it is not possible to predict certainly in which of the tuberculized individuals the tuberculous infection will proceed to harvest, that is to say, in whom the tuberculous infection will yield clinical evidence of its presence, it seems simple prudence, based on sound science, that an attempt should be made in the case of each individual to register the fact of infection (now readily determined by bacteriological method) and approximately the date when infection is contracted.

And if it can be shown that there are simple means whereby tuberculization can be met by *de*tuberculization, and that those means are effective in proportion as they are applied betimes, and that the means, while effective, are unaccompanied by risk, it would seem desirable that such means of *de*tuberculization should be adopted in the individual case as soon as practically possible after the fact of tuberculization has been determined.

That is what it has been my endeavor to realize in the practice of *anticipatory detuberculization.*

The procedure to be followed may be conveniently illustrated by a short statement of the method used by me in private and institutional practice.

Assuming that one member of a household is found to be suffering from evident tuberculous disease, the injunction is that every member of the family, and conspicuously every child, should be subjected, in addition to a clinical examination, to a tuberculin test and the result thereof carefully noted. The tuberculin test may be that of Pirquet or, more suitably in young children, that of Moro (inunction). The latter method has not only the obvious advantage of simplicity and less disturbance to the child, but meets the objection of parents to scarification. By whatever method, the purpose is readily reached. In many cases a positive result will be obtained at the first test. In the event of negative result, the procedure will be repeated after a given interval and again, say, every 3 or 6 months, until a positive result is obtained. The date of the latter should be registered. The procedure is readily carried out by private practitioners or by medical officers attached to an institution.

So convinced am I as to the high value of the determination for the after-history of the individual, that the procedure should, in my opinion, be regarded under present conditions as *routine* duty in respect of children from early infancy onward. Having regard to the facts on which

the procedure is based, the determination of the moment when the individual becomes tuberculized forms, under existing communal conditions, one of the most significant facts in his life-history.

After tuberculization has been determined, there arises the question of anticipatory *de*tuberculization.

The child is tuberculized. His doctor knows it and, given sufficient intelligence and education, his parents or guardians will share the knowledge and appreciate its significance. Henceforward his environment, in the largest sense, will be reviewed from that point of view. Apparent delicacy and actual illness will be interpreted in the light of the knowledge. Clinical observation will be quickened and sharpened. Nutrition will be watched and growth will be followed with awakened interest. The child's glandular and neuromuscular systems will be viewed with care. At stated intervals the developing child will be overhauled, with the fact of his tuberculization in mind. In this way the first buddings of tuberculous disease will not fail to be detected.

This is a profoundly significant application of preventive medicine. Can we go further? Can we meet tuberculization by *de*tuberculization? In answering the question in the affirmative, I assume that the antigenic action of tuberculin is admitted. In my own mind—as the result of uninterrupted experience in its use, extending over thirty years—there remains no doubt on that point. There is similarly little doubt that the efficacy of the antigen is proportionate to its *timely* use. The attitude of hesitancy and negation, prevalent in many quarters, is largely due to uncertainty as to purpose and delay in its exhibition, until conditions which form indications for its use have been replaced by those in which its value is minimal or its use even contraindicated.

In a protracted infection like tuberculosis, with alternating advance and recession, antigenic effects must be sought *early* in relation both to the initial infection and to subsequent recurring advances.

My practice has been to institute treatment by tuberculin, tentatively, at the date when the fact of tuberculization is first established, and particularly later when, along with a positive tuberculin reaction, there is clinical evidence of tuberculous disease, even if this be slight in degree; for instance, minor enlargement of lymph nodes, muscular dystrophy and hypotonus, disturbance of nutrition, etc. Tuberculin treatment for this purpose is most conveniently carried out by percutaneous method as recommended by me elsewhere (*British Medical Journal*, March 24, 1923).

The results of continued observation during the past fourteen years have satisfied me as to the value of the percutaneous exhibition of tuberculin.

The effects are not limited to those which are obvious when the application is made locally in the neighborhood of a tuberculous process, as, for instance, at the edge of a lupus patch or over a tuberculous lymph node. Tuberculin exhibited percutaneously is freely absorbed through the skin, and in tuberculous subjects, in proportion to the amount absorbed, results are obtained which may be grouped as local, focal and general or systemic.

The *local* reaction is usually well-marked and serves to some extent as an index of the patient's response to treatment. The intensity of local reaction may be used to gauge further dosage (amount, interval, etc.).

Focal and *systemic* effects are seldom pronounced. This is as one might expect, having regard to the slower absorption of tuberculin through the skin tissues as compared with its rapid dissemination when administered subcutaneously. The curative influence is thus exerted in more gradual, prolonged fashion. This has appeared to me all to the good in respect of the curative influence, and the risk of overdosage is excluded. The focal changes are readily observed in surface lesions, wherever situated, such as lupus, scrofuloderma, discharging sinuses, tuberculous laryngitis, etc. They may be determined less certainly within the lung and other viscera by physical examination. The systemic reaction does not commonly involve much pyrexic disturbance.

The procedure I recommend is based on those facts. Having determined by percutaneous test that the child is tuberculized, the percutaneous exhibition is continued week by week or at such intervals as the circumstances indicate. The curative influence is readily followed in those cases which already present superficial tuberculous foci, such as enlarged lymph nodes. Glandular agglomerations are progressively reduced and resolved into individual discrete nodes, each of which becomes gradually smaller until a mere fibrous remnant is traceable.

The beneficial influence—the *de*tuberculizing effect—is not limited to obvious foci but extends more widely through the system. It is manifested by general improvement in health and condition. Indications of malnutrition and muscular dystrophy are replaced by healthy aspect and increased size and tone of muscle. The neuromuscular system is disintoxicated. Gain in weight from week to week is commonly registered in cases in which previously the weight had been decreasing or stationary.

Our records include many children in whom the evidence of effective *de*tuberculization has been most arresting.

In the elaboration of the percutaneous method I have used various turberculins in a variety of excipients. Koch's original tuberculin and Beraneck's tuberculin give satisfactory results. The tuberculin may be exhibited in varying strengths from 10 to 50. Lanolin and vaseline in combination form a suitable excipient, or *eucerin*, that is, a mixture of 5 parts of oxycholesterine from wool-fat and 95 parts of paraffin ointment. The addition of eucalyptol in small amount ensures the conservation of the ointment as in the following formula:

℞ Tuberculin (Orig. K.).....10–50 per cent
Eucalyptol..... 5 per cent
Eucerin.....ad 100

Misce bene

Sig: Tuberculin ointment, with caution

For the purposes of continuous *de*tuberculization the percutaneous method has obvious advantages over hypodermic and intracutaneous methods of exhibition. The weekly inunction is a simple affair, not an operation in the mind of patient or parent. The dread of the recurring puncture is excluded. The local (skin) reaction causes little discomfort. The procedure interferes in no way with the child's ordinary life.

The development of results affords occasion for fascinating study. The process is suitably described as *de*tuberculization. In the child the striking recession of symptoms and convincing indications of heightened resistance, with its promise for the future, seem amply to warrant the term, *Anticipatory Detuberculization.*

THE HOME HOSPITAL

AN EXPERIMENT IN TREATING TUBERCULOSIS AS A FAMILY PROBLEM

JAMES ALEXANDER MILLER AND JOHN C. GEBHART[1]

In its work with families in which either the father or mother is afflicted with tuberculosis, the New York Association for Improving the Condition of the Poor has always sought to stand in the breach and to hold the family together while the patient himself is fighting his battle with the disease. When tuberculosis invades the home the usual recourse is to place the patient, either the father or the mother, in a sanatorium and to place the children in a preventorium, in a foster home, or with friends or relatives. Separated from his loved ones, the patient becomes worried and discouraged, a factor which alone retards his progress; or he is likely to leave the sanatorium before a complete recovery has been effected. If there ever was a disease in which the family and not merely the patient is the unit of treatment, that disease is tuberculosis.

It was to meet this situation adequately that Mr. John A. Kingsbury, then General Director of the A. I. C. P., conceived the idea of the Home Hospital. It was accordingly established by the A. I. C. P. in March, 1912, for the care of tuberculous families. The Home Hospital is a demonstration of the results which can be secured by housing the tuberculosis patient and his family in a wholesome environment, by supplying the family with sufficient relief to provide for an adequate standard of living and by providing the necessary medical and nursing care not only to insure the recovery of the patient but to prevent tuberculosis from occurring among those members of the family who had not previously been afflicted.

There are obvious and perhaps insuperable difficulties in managing the disease in this way in any but the most highly concentrated communities. Peers has grappled with the problem in his Colfax School for the Tuberculous, which is fundamentally a sanatorium with accom-

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modations for families of patients, and arranged with the idea of educating well members of the families as well as the patients in the routine treatment of tuberculosis, but the Colfax School is attended by families who are well able themselves to pay for this expensive and elaborate treatment, while the Home Hospital is restricted for the most part to dependent families.

OBJECTIVES OF THE HOME HOSPITAL EXPERIMENT

When the Home Hospital was first undertaken four main objectives were conceived, and these have been kept constantly in mind during the progress of the experiment. The experiment, therefore, may be said to have succeeded in the degree to which each of these four objectives has been accomplished. Briefly, the four objectives are to prove that

1. Tuberculosis can be treated as successfully in New York City as in remote sanatoria.
2. The family, as a social unit, can be kept intact.
3. No healthy members of the family need acquire tuberculosis through contact with tuberculosis patients.
4. The Home Hospital can be maintained at a cost which is comparable to the cost of similar care in sanatoria and preventoria.

One section of the East River Homes, a model apartment house, was taken over in March, 1912, to house such families and to provide headquarters for the medical and nursing service. This space was twice increased, until in 1916 facilities for 80 families were available. With the sudden withdrawal of city funds for indigent tuberculosis patients referred by the Department of Public Charities, the A. I. C. P. was forced to curtail considerably the size of the Home Hospital. Through the generosity of Mrs. Elizabeth Milbank Anderson the Victoria Apartments were purchased in 1918, providing for 20 families. Though greatly reduced in size, all of the essential features of the original plant were maintained.

A report of ten years' experience with the Home Hospital has just been published by the A. I. C. P.[2] During this period, 469 patients, of whom 306 were adults and 163 were children, have been discharged

[2] *Tuberculosis, a Family Problem. The Story of the Home Hospital of the A. I. C. P.*, by John C. Gebhart, issued by the New York Association for Improving the Condition of the Poor, 105 East 22nd Street.

from the Home Hospital. For a detailed account of the methods employed and the selection of cases we must refer the reader to that report. A brief description of the type of families received at the Home Hospital is needed, however, before really valid comparisons can be made with other institutions. For the most part these families have suffered complete economic breakdown before admission to the Home Hospital, since they are largely recruited from families who have applied to the A. I. C. P. or other agencies for relief. Most of the wage-earners have followed occupations such as laborers, truck-drivers and other unskilled trades, which call for a great expenditure of physical energy with a correspondingly low income. Only too frequently the men have continued at these occupations for long periods after tuberculous infection had made considerable headway. The great majority of the families are of foreign birth, largely Irish and Italian. The average size of the family (5.1 persons per family) is considerably larger than that prevailing throughout the country. It must also be pointed out that after discharge from the Home Hospital most of the families are obliged to return to their former occupations and to the typical New York tenement home.

ADULTS

The adult patients were classified with respect to condition on admission as either incipient, moderately advanced or far advanced. On discharge they were classified as either quiescent (including arrested and apparently arrested), improved, unimproved or dead.

In the selection of cases preference is given to those whose prognosis is hopeful. This has resulted in a slightly greater proportion of cases which were incipient on admission than that found in most other sanatoria. Of those institutions whose records were available, the sanatorium conducted by the Metropolitan Life Insurance Company at Mt. McGregor, New York,[3] alone exceeded the Home Hospital in incipient cases. In the latter institution the proportion of incipient cases has steadily increased, from the beginning in 1914, when 28.3 per cent were incipient, to 1920, when 70 per cent were incipient. Obviously this fact must be kept in mind in interpreting the results of various institutions. In table 1 is a

[3] *The After-History of 953 Tuberculous Patients Discharged from the Metropolitan Life Insurance Sanatorium from 1914 to 1920,* Howk, Dublin and Knudsen, AMERICAN REVIEW OF TUBERCULOSIS, 1922, vi, 707.

comparison of the proportion of incipient, moderately advanced and far advanced patients in the Home Hospital and other institutions.

We have attempted to compare our results with those of certain well-known institutions covering a considerable period of time. In the report of the Metropolitan Life Insurance Company, previously referred to, comparison was made of the results of the treatment offered at Mt. McGregor Sanatorium, maintained by the Metropolitan, and those of Trudeau, Loomis, and King Edward VII. In table 2 the results at Home Hospital have been added to the previous report.

In general, results secured at Home Hospital are quite comparable to those secured at Mt. McGregor, the sanatorium conducted by the Metropolitan Life Insurance Company. The fact that Mt. McGregor reports a slightly larger porportion of cases "improved" than the Home

TABLE 1

Condition of patients on admission at Home Hospital compared with other institutions

CONDITION ON ADMISSION	TRUDEAU		LOOMIS		KING EDWARD VII		MT. MCGREGOR		HOME HOSPITAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total number of cases	1,892	100	1,192	100	1,707	100	1,319	100	306	100
Incipient	534	28.2	153	12.8	460	26.9	738	56.0	157	51.3
Moderately advanced	1,254	66.3	471	39.5	848	49.7	493	37.3	97	31.6
Advanced	104	5.5	568	47.6	399	23.4	88	6.7	47	15.3
Not stated	0		0		0		0		5	1.6

Hospital is rather due to a different use of the term on the part of the physician than to a significant variation in results obtained.

With respect to results secured among the patients who were diagnosed incipient on admission the Home Hospital is only exceeded by King Edward Sanatorium. For those diagnosed moderately advanced on admission both Trudeau and King Edward show slightly better results. It must be pointed out, however, that the practice in both of these institutions is to discharge their patients before they are in a moribund condition. This practice obviously results in fewer deaths reported within the institution. For those who were far advanced on admission only Mt. McGregor and Home Hospital are at all comparable, and these two institutions report practically identical results. The high mortality to be expected in treating advanced patients is undoubtedly concealed in the case of the other sanatoria by the early discharge of dangerously ill patients.

TABLE 2

Comparison of results achieved on discharge according to condition on admission at Home Hospital and four sanatoria

CONDITION ON DISCHARGE	TRUDEAU		LOOMIS		KING EDWARD VII		MT. MCGREGOR		HOME HOSPITAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
All cases										
Total number of cases	1,892	100	1,192	100	1,707	100	1,018	100	306	100
Quiescent	1,285	67.9	496	41.6	1,080	63.3	632	62.1	195	63.7
Improved	287	15.2	335	28.1	330	19.3	229	22.5	30	9.8
Unimproved	307	16.2	258	21.7	297	17.4	92	9.0	48	15.6
Dead	13	0.7	103	8.6	0	0	65	6.4	29	9.4
Not stated	0	0	0	0	0	0	0	0	4	1.3
1. Incipient on admission										
Total number of cases	534	100	153	100	460	100	592	100	157	100
Quiescent	408	76.4	114	74.5	427	92.8	478	80.7	132	84
Improved	73	13.7	32	20.9	16	3.5	88	14.9	14	8.9
Unimproved	52	9.7	7	4.6	17	3.7	19	3.2	8	5.0
Dead	1	0.2	0	0	0	0	7	1.2	1	0.6
Not stated	0	0	0	0	0	0		0	2	1.2
2. Moderately advanced on admission										
Total number of cases	1,254	100	471	100	848	100	366	100	97	100
Quiescent	847	67.5	257	54.5	555	65.4	152	41.5	57	58.8
Improved	185	14.8	112	23.8	160	18.9	133	36.4	13	13.4
Unimproved	212	16.9	80	17.0	133	15.7	48	13.1	19	19.5
Dead	10	0.8	22	4.7	0	0	33	9.0	6	6.1
Not stated	0	0	0	0	0	0	0	0	2	2.1
3. Far advanced on admission										
Total number of cases	104	100	568	100	399	100	60	100	47	100
Quiescent	30	28.8	125	22	98	24.6	2	3.3	5	10.6
Improved	29	27.9	191	33.6	154	38.6	8	13.3	2	4.2
Unimproved	43	41.3	171	30.1	147	36.8	25	41.7	21	44.8
Dead	2	2.0	81	14.3	0	0	25	41.7	19	40.4

CHILDREN

Particular attention has been given to children, for we have assumed that all have been in close contact with the patient and that all were likely to develop active tuberculosis unless preventive measures were

taken. Those children who exhibited the following symptoms: (1) underweight for age, (2) constant or frequent cough, (3) occasional or constant elevation of temperature of undiscoverable origin, (4) râles (near one or both nipples, constant or inconstant), interscapular dulness and positive Pirquet reaction (under four years), were considered patients, and received more intensive follow-up attention. During the period covered, 978 children were admitted. Of these, 281 were diagnosed "good," 534 as "suspects," and 163 as patients. Of the 163 patients, 151, or 92.5 per cent, were discharged either in "good condition," "improved," "quiescent," or "negative;" 3, or 1.8 per cent, were fair or poor; 1 was progressive; 2, or 1.2 per cent, had died; and for 6, or 3.6 per cent, no adequate diagnosis on discharge was recorded.

When the Home Hospital idea was first conceived the objection was made by some that without complete segregation of the tuberculous many new cases would develop within the institution itself. In our ten years' experience no new cases of tuberculosis, either of children or adults, have developed while a family was in the institution. This remarkable record we attribute to the educational work with families as to the importance of fresh air and sunlight, and to simple precautions regarding sleeping arrangements and the use of common towels, glasses and dishes.

CONDITION OF ADULT PATIENTS AFTER DISCHARGE

But it is not enough to discharge a tuberculosis patient as "quiescent" or "improved." The effect of the treatment must be such as to provide a reasonable assurance against a relapse, which is likely to result either in diminished earning capacity or in early death. This objective from the first has been recognized as of prime importance in the Home Hospital. It has been our conviction that by dealing with the family as a unit, and not simply with the patient, we should be able to establish a standard of living and habits of personal hygiene which would follow the family after its discharge from the institution. In order to test the permanent effect of Home Hospital treatment, we have followed up the after-histories of all but the most recently discharged cases within the period under consideration.

The attempt to discover whether or not the patient had suffered a relapse subsequent to discharge was abandoned, because of the difficulty of getting reliable statements based on a doctor's diagnosis. We had, therefore, to content ourselves with finding answers to two questions:

(1) How many of the discharged patients died subsequent to discharge? (2) How many of those alive at the time of the follow-up were able to work? Despite the many difficulties of conducting an inquiry of the 277 discharged patients, only 15, or 5.5 per cent, either could not be located or refused information.

In table 3 we have summarized the results of this follow-up. The average period of time elapsing since discharge was 3.2 years, with a

TABLE 3

After-history of discharged adult tuberculosis patients of the Home Hospital

CONDITION ON DISCHARGE	TOTAL CASES		DEAD		ABLE TO WORK		NOT ABLE TO WORK	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total	262	100	71	27.1	157	59.9	34	12.8
Quiescent	186	100	26	14.0	148	79.6	12	6.4
Improved	26	*	13	*	5	*	8	*
Unimproved	46	*	30	*	2	*	14	*
Not stated	4	*	2	*	2	*		

* Percentage not calculated because of small numbers.

TABLE 4

After-history of discharged adult tuberculosis patients of the Home Hospital by period of follow-up

PERIOD OF FOLLOW-UP	TOTAL		ABLE TO WORK		NOT ABLE TO WORK		DEAD	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total	262	100	157	59.9	34	12.8	71	27.1
Less than 3 years	108	100	44	40.7	12	11.1	52	48.1
Three years and less than six	124	100	89	71.7	21	16.9	14	11.3
Six years and less than nine	26		24		1		1	
Not stated	4		0				4	

range of from 6 months to 9 years. This fact must be kept clearly in mind in evaluating these results, for it is in the first year after discharge that the mortality is highest.

Obviously, the results of the follow-up are dependent on the period of time elapsing since discharge. While our data are too meagre to permit a detailed study by years, we have, in table 4, compared the results for three-year periods. A glance at this table will indicate that the chances of death are greatest in the early years after discharge and the chances of those surviving being able to carry on effectively are greatest in the later years.

The results of Home Hospital treatment in prolonging the life-span and in restoring the earning capacity of the patient may now be compared with the results secured by leading sanatoria in America. In a recent study by the National Tuberculosis Association the results of the follow-up of 12,708 patients discharged from American sanatoria are given.[4] The report of the Metropolitan Life Insurance Company, previously cited, gives the results of its follow-up. After excluding cases which could not be reached the comparison as shown in table 5 is made.

Thus the results secured by the Home Hospital are not quite so good as at Mt. McGregor but distinctly better than those of other sanatoria. A word of explanation is needed. The results of the study by the

TABLE 5

Comparison of the condition of discharged patients from 13 leading sanatoria surveyed by the National Tuberculosis Association, Mt. McGregor, and Home Hospital

STUDY	TOTAL CASES		DEAD		ABLE TO WORK		NOT ABLE TO WORK	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
National Tuberculosis Association	12,708	100	6,100	48	4,073	39	1,426	13
Mt. McGregor	896	100	87	9.7	719	80.2	90	10
Home Hospital	262	100	71	27.1	157	59.9	34	12.8

National Tuberculosis Association are largely determined by the great number of patients who were far advanced on admission. A recent tabulation by that organization for 1920 indicated that 50 per cent of the patients were advanced cases on admission. On the other hand, it is difficult to explain why nearly three times the proportion of patients died after discharge from Home Hospital as from Mt. McGregor. The social and economic status of the different groups must, we fancy, go far toward explaining this difference. Discharged cases from Mt. McGregor were immediately returned to their positions with the Metropolitan Life Insurance Company, whereas no such security of tenure could be assured our discharged patients. Moreover, provision is made for the immediate readmission of relapsed cases discovered through careful periodic medical examinations, with a corresponding effect on the death-rate.

[4] *Sanatorium Follow-up Studies*, Dorothy E. Wiesner, AMERICAN REVIEW OF TUBERCULOSIS, 1922, vi, 320.

CHILDREN

The proportion of children found to have died or to be totally incapacitated on follow-up was much smaller than in the case of adults. While this is undoubtedly due in a large measure to the permanent effect of Home Hospital care it must also be attributed partly to the fact that among the general population death-rates at these ages are at their lowest point, and total incapacity because of illness is very rare. These results are summarized in table 6.

It may be pointed out that again the greatest risk is soon after discharge, for all of the deaths occurred in the group followed up for three years only.

TABLE 6

Condition of discharged Home Hospital patients (children under 16) on follow-up

TOTAL		DEAD		ABLE TO WORK		NOT ABLE TO WORK	
Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
148	100	3	2	139	94	6	4

TABLE 7

	COST PER FAMILY PER DAY		COST PER INDIVIDUAL PER DAY		COST PER "AMMAIN" PER DAY	
	Home Hospital	Tuberculosis division	Home Hospital	Tuberculosis division	Home Hospital	Tuberculosis division
Medical and nursing service	$1.903	$ .178	$ .366	$ .031	$ .676	$ .055
Total living costs	5.026	3.226	.967	.558	1.786	1.005
A. I. C. P. contribution	2.459	.718	.473	.124	.874	.224
Family earnings	2.403	2.241	.462	.388	.854	.698
Other sources	.168	.267	.031	.046	.058	.083
Total cost	6.929	3.404	1.333	.589	2.462	1.060

COSTS

It will readily be inferred that, so far as A. I. C. P. funds are concerned, the Home Hospital plan is by far the most costly, as table 7 clearly indicates.

The "Ammain" is a value which reduces the expenditures of all families to the common denominator of the adult male. The "cost per ammain per day" represents in each instance the cost of maintaining a man at his period of "maximum economic demand." The costs

of each plan are therefore placed on a comparable basis, since variations in size of family and the age and sex of the individuals are avoided. From these figures it is obvious that the intensive Home Hospital care involves a far greater expenditure of the Association's funds than the plan which involves less intensive work and in which the total cost of the family's care is shared with sanatoria, preventoria and other institutions.

We have made an attempt to secure reliable up-to-date estimates of such costs, but with little success. On the basis of such data as we were able to secure, we may safely say that when the patient is a widow with three dependent children the cost of Home Hospital care would be about $4.76 a day, while to place her in a sanatorium and the children in institutions, usually the only alternative, would involve a daily cost of at least $4.21, a difference of only 13 per cent. In the interest of more continuous and satisfactory treatment and for the social welfare of the family itself this cost is more than justified.

CONCLUSIONS

The success of the Home Hospital experiment must be judged, we believe, by the degree to which the four objectives laid down in the beginning have been accomplished.

1. The experiment has definitely proved that tuberculosis patients can be quite as successfully treated in New York City as in remote sanatoria and hospitals.

2. The family has been kept intact and made the unit of preventive and educational work.

3. During the ten-year period no healthy person has acquired tuberculosis during residence at the Home Hospital through contact with tuberculosis patients.

4. When the complete cost of underwriting family living expenses and of supplying both preventive and sanatorium care is met, the Home Hospital plan involves no greater expenditure than that involved in breaking up the family and sending the patient to a sanatorium or hospital.

FURTHER REMARKS ON MUTATION OF PULMONARY SHADOWS DUE TO TYPE OF BREATHING

H. A. BRAY[1]

In a previous communication (1) I drew attention to the occurrence of shadow mutations on the chest roentgenogram in tuberculosis when X-ray exposures were made of the same patient, first at the height of costal and then at the height of diaphragmatic inspiration. The shape of the lesion changes with the type of breathing employed, and I attributed the mutations to this fact.

The mutations noted by this method were at times so striking that attempts to interpret them in pathological terms proved highly confusing. This observation led me to suggest that it would perhaps be better, at least for the present, to use descriptive rather than pathological terms for the interpretation of pulmonary shadows.

Louisa T. Black (2), following the technique advised, recently attempted to corroborate my observations for the purpose of obtaining "more detailed data on tuberculosis patients, and if possible, from this information to arrive at a more standardized technique for taking chest roentgenographs." Her study included 36 tuberculosis patients, in 11 of whom anterior as well as the usual posterior exposures were made. In only 3 instances among the 36 were the mutations sufficiently evident to deserve comment. Miss Black, from her studies, concludes:

> In spite of these findings, and as a result of a general survey of the situation, considering the diagnostic value of these differences and the economic side of the question, it can hardly be recommended that, for general diagnostic purposes in pulmonary tuberculosis, more than one type of position and inspiration be used. The matter of choice for general use rests entirely with the individual case. For purely academic or research purposes, however, and to obtain the maximum detailed information on an individual case, it is recommended that at least both types of inspiration be used and, if possible, the two positions, posterior-anterior and anterior-posterior, be taken.

[1] New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

The reproductions illustrating Miss Black's article unfortunately leave much to be desired in clearness of detail, and render their study somewhat difficult. However, the reproductions of diaphragmatic breathing when compared with those of costal apparently show no marked difference in the respective levels of the diaphragmatic shadow. If this be true, it would adequately explain the infrequency of the shadow mutations noted by Miss Black. The mutations are due to the change in the shape of the pulmonary lesion incident to a relatively pure type of costal inspiration on the one hand, and diaphragmatic on the other. When the type of respiration is relatively pure, the roentgenograph will usually reveal a disparity of at least an inch and a half in the respective levels of the diaphragmatic shadows. On the other hand, if this disparity is but slight it means that the inspirations were more or less of the mixed type and, as a consequence, the shape of the lesion is not sufficiently altered to produce manifest mutations.

It is essential for the proper demonstration of the mutations to instruct patients to employ alternately the two types of breathing, an arduous task. In fact, a fairly large number of patients apparently are unable to coöperate properly, even after considerable practice. Furthermore, and this is an important point, inspection alone is not an accurate guide to the purity of the type of breathing, since in certain patients attempting to breathe diaphragmatically the diaphragm does not descend, although the abdomen may be protruded. This fact may be readily verified by fluoroscopic examination, and we have found it helpful to measure the excursion of the diaphragm by fluoroscopic observation previous to making the X-ray exposure. These difficulties preclude the method as a routine procedure, a point mentioned by Miss Black and one with which I agree.

The mutations noted by Miss Black were found only in patients suffering from advanced disease, an unexpected result, since the loss of pulmonary expansion imposed by the advanced disease usually does not permit the lesion to change its shape sufficiently to produce evident shadow mutations. Likewise, conditions which materially interfere with costal or diaphragmatic inspiration, such as rigidity of the chest-wall, or adhesions of the diaphragm, prevent a satisfactory demonstration of the mutations. Our experience has been that the mutations are more striking in patients with early or moderately advanced disease, particularly the latter, owing to the better definition of the pulmonary shadows.

Recently a further study was made for evidence of shadow mutations in 32 tuberculosis patients, of whom 11 were in the early, 19 in the moderately advanced, and 2 in the advanced stage of the disease. In this series, the classification of the disease was made on the physical signs alone. The X-ray exposures were posterior; anterior ones were not attempted for reasons mentioned in the previous communication. Six among this number were unable to coöperate properly after considerable instruction. The X-ray films of the remaining 26 showed evidence of shadow mutations, more striking in some than in others. From my previous and present studies, it would seem that with proper coöperation of the patient and the exclusion of certain conditions above referred to, mutations are the rule rather than the exception among tuberculosis patients.

The accompanying twelve illustrations are among the best examples of mutations occurring in this series. They illustrate a variety of roentgenographic mutations commonly encountered among adults suffering from chronic pulmonary tuberculosis. From their study one is impressed by the necessity for reserve when attempting to define the shadows in pathological terms.

Certain technical points, not mentioned in the previous communication, have been referred to, and may be helpful to those interested in the demonstration of these mutations.

REFERENCES

(1) Bray, H. A.: Mutations of pulmonary shadows due to type of breathing, Amer. Jour. Roentgenol., October, 1922.

(2) Black, L. T.: The technique of chest roentgenography in pulmonary tuberculosis, Amer. Rev. Tuberc., 1923, viii, 371.

FIGS. 1a AND 1b. CASE 7672. MODERATELY ADVANCED STAGE

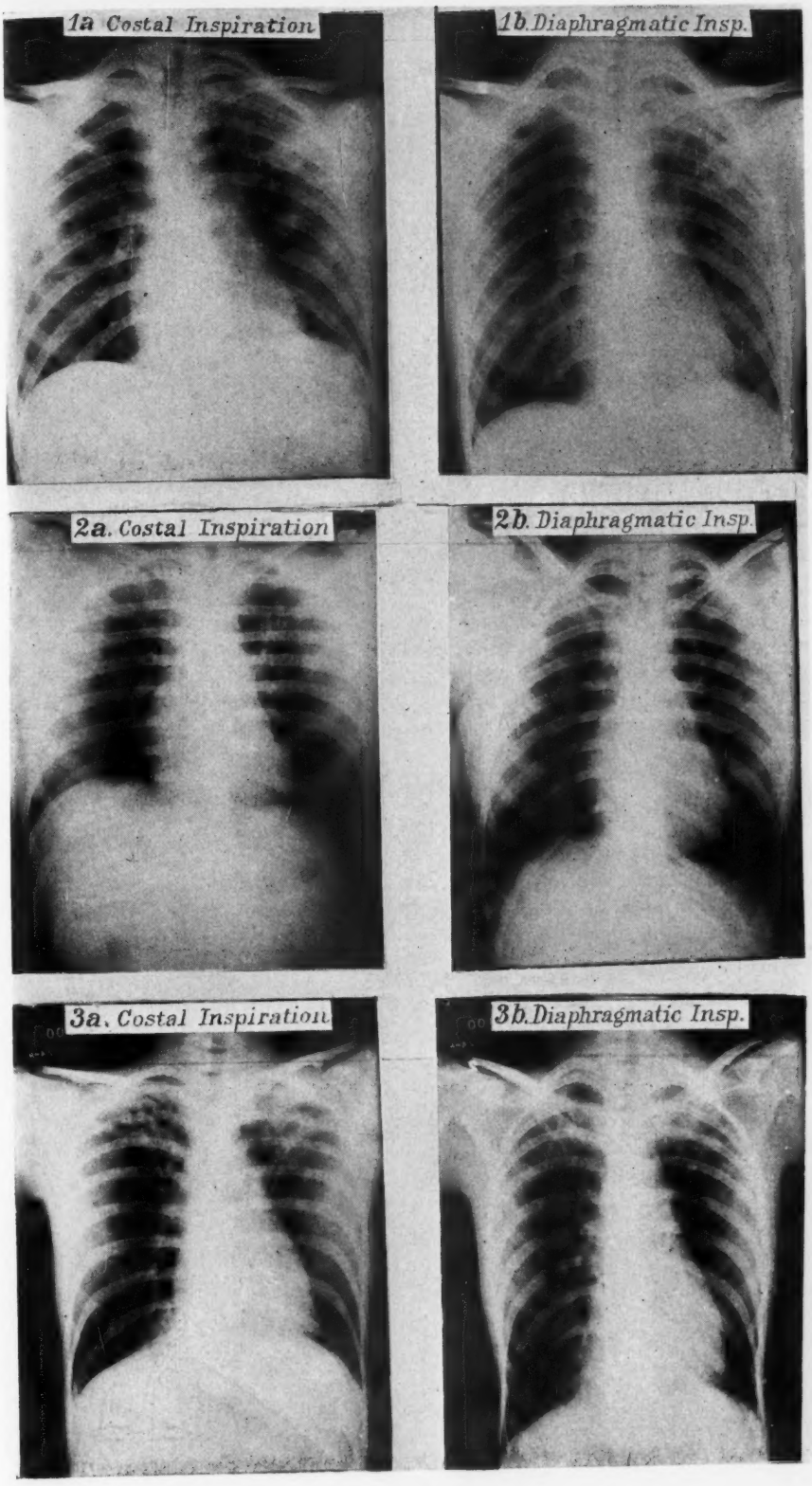
Comparison of fig. 1a, costal, with fig. 1b, diaphragmatic inspiration, shows a striking difference in the outline of the thorax and of the heart and in the respective levels of the diaphragmatic shadows. When these features are in definite contrast, as observed in all the accompanying illustrations, it indicates that the inspirations were of a relatively pure type. Note particularly the difference in the appearance of the two contiguous rings and the adjacent shadows in the upper half of the left lung field.

FIGS. 2a AND 2b. CASE 7574. MODERATELY ADVANCED STAGE

The hilar shadows in fig. 2a, costal, are larger and denser than in fig. 2b, diaphragmatic inspiration, as are also the linear markings in their immediate neighborhood. Likewise, the shadows in the upper third of both lung fields in fig. 2a appear much denser, particularly at the summit. The greater distribution and density of the shadows at the top of the lung field frequently noted on costal breathing may be due to the fact that with this type of inspiration the expansion of the apex of the lung is upward, while on diaphragmatic inspiration it is downward.

FIGS. 3a AND 3b. CASE 7800. MODERATELY ADVANCED STAGE

In fig. 3a, costal inspiration, the shadows occupying the upper third of both lung fields would be described as "soft" in appearance, a term which to many observers denotes a progressive type of lesion. In fig. 3b, diaphragmatic inspiration, many of these "soft" shadows have been converted into "hard" rope-like shadows, which are said to represent retrogressive processes in the lung. The right hilar shadow in fig. 3b reveals small circumscribed shadows of marked density, which in fig. 3a are barely perceptible. Note also the difference in the respective levels and outlines of the diaphragmatic leaves.


1a Costal Inspiration
1b. Diaphragmatic Insp.
2a. Costal Inspiration
2b. Diaphragmatic Insp.
3a. Costal Inspiration
3b. Diaphragmatic Insp.

FIGS. 4a AND 4b. CASE 7357. INCIPIENT STAGE

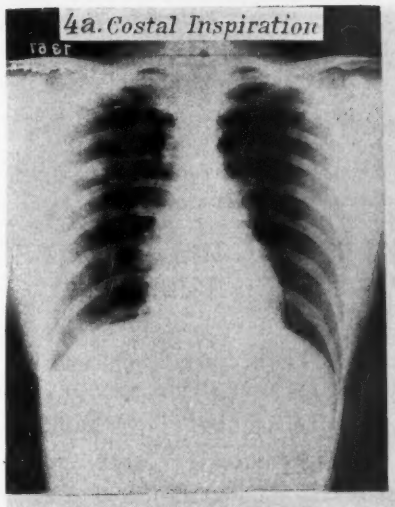
Fig. 4a, costal, and fig. 4b, diaphragmatic inspiration. The mutation of the shadows in the upper half of the right lung field is so marked that it is difficult to realize that this change is due solely to a difference in the shape of the lesion incident to the type of breathing. In fig. 4a they are characterisically "soft" in appearance and in fig. 4b they are unquestionably "hard". Unfortunately the X-ray prints fail to show this difference as clearly as the original films.

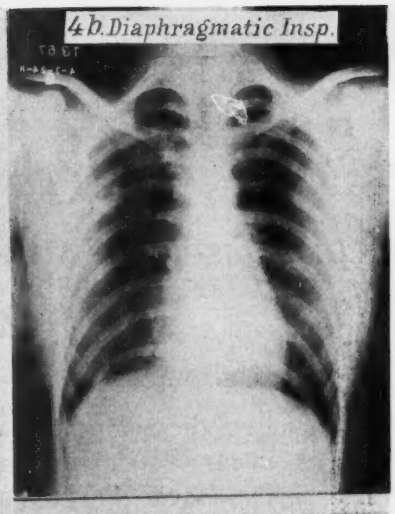
FIGS. 5a AND 5b. CASE 7712. MODERATELY ADVANCED STAGE

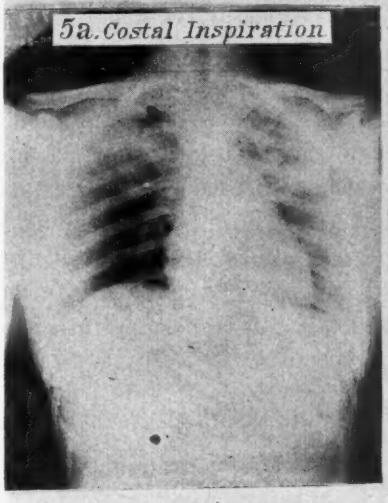
Fig. 5a, costal, and fig. 5b, diaphragmatic inspiration. A glance at the lung fields is sufficient to reveal the degree of mutation which the pulmonary shadows may at times undergo with the two types of inspiration. One cannot reasonably assume that the mutations are the result of a corresponding change in the pulmonary lesion, since it is inconceivable that such a condition could arise in the space of a minute, the time-interval between the X-ray exposures. Here, indeed, is a striking example of the difficulty of interpreting pulmonary shadows in pathological terms.

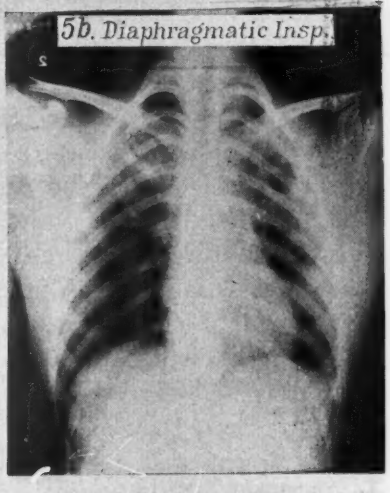
FIGS. 6a AND 6b. CASE 7721. INCIPIENT STAGE

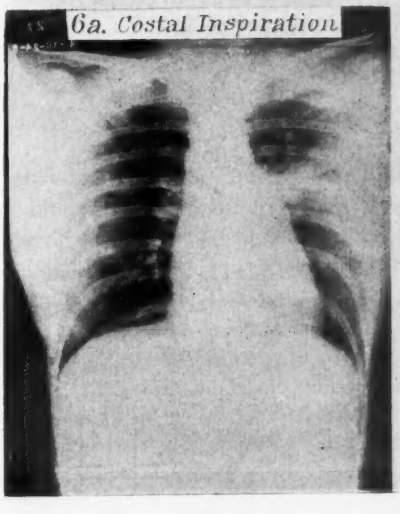
Fig. 6a, costal, and fig. 6b, diaphragmatic inspiration. The striking feature is the marked mutation of the dense shadow passing from the region of the left hilum outward into the lung field. One is impressed by the greater distribution and density of this shadow in fig. 6a as compared with that in fig. 6b.

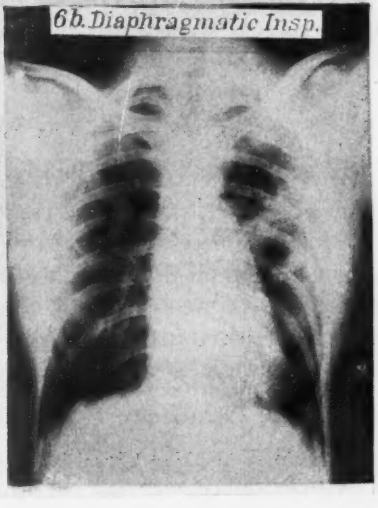

4a. Costal Inspiration


4b. Diaphragmatic Insp.


5a. Costal Inspiration


5b. Diaphragmatic Insp.


6a. Costal Inspiration


6b. Diaphragmatic Insp.

A COMPARISON OF THE SCHULTE-TIGGES AND ZIEHL-NEELSEN METHODS OF STAINING TUBERCLE BACILLI

ORA M. MILLS[1] AND PEARL L. KENDRICK[2]

In a study of the comparative value of the Schulte-Tigges and Ziehl-Neelsen methods for staining tubercle bacilli, Shoub (1) recently reported results highly in favor of the former method. In a total of 880 examinations, this author found 244 positive preparations by the Schulte-Tigges and 183 by the Ziehl-Neelsen method. When estimating the number of bacilli exposed according to Gaffky's scale, this author observed five times as many by the Schulte-Tigges as by the Ziehl-Neelsen method.

In view of Shoub's findings, a series of comparative examinations between the Ziehl-Neelsen and Schulte-Tigges methods was undertaken at both the Lansing laboratories and the Houghton branch laboratory. Since the Ziehl-Neelsen method was being employed as a routine procedure in these laboratories, it seemed important to make these examinations and, if our results warranted, to consider substituting the Schulte-Tigges method in our routine procedures.

The tests were carried out by each author without knowledge that similar tests were being made by the other. After the data had been collected and compared, the results in both groups of examinations were found to be practically the same. Since our results were not found to be in agreement with those of Shoub, it has seemed of interest to present this brief report.

TECHNIQUE

The sputa were first autoclaved and the supernatant fluid removed. A double set of preparations was made on slides from the sediments. An amount of sediment necessary for both preparations was placed with a heavy platinum loop on the first slide and thoroughly mixed, and half was then transferred to the second slide, making the two preparations as comparable as possible.

[1] Michigan Department of Health, Branch Laboratory, Houghton, Michigan.
[2] Michigan Department of Health, Bureau of Laboratories, Lansing, Michigan.

The following are the staining procedures employed:

Ziehl-Neelsen method

1. Steam 5 minutes in carbol-fuchsin
2. Wash in water
3. Decolorize in acid-alcohol (3 per cent HCl in 95 per cent alcohol)
4. Wash in water
5. Counterstain with Loeffler's methylene-blue
6. Wash and dry

Schulte-Tigges staining method (2)

1. Steam one minute in carbol-fuchsin
2. Wash in water
3. Decolorize with 10 per cent sodium sulphite (solution renewed twice a week)
4. Wash in water
5. Counterstain with saturated aqueous solution of picric acid
6. Wash and dry

The results with the two methods with 700 specimens are summarized in the following table:

Findings with 700 sputa

STAINING METHOD	ZIEHL-NEELSEN	SCHULTE-TIGGES
Number positive	190	190
Total number bacilli exposed (Gaffky's scale)	4363	5285
Number negative	510	510

In 200 of the specimens recorded, a third comparative examination was made by Much's method. Of these examinations, 89 were positive compared with 88 by both the Ziehl-Neelsen and Schulte-Tigges methods. The total number of bacilli exposed according to Gaffky's scale by Much's method was 1493 compared with 1327 by the Ziehl-Neelsen and 1447 by the Schulte-Tigges. In the case of the additional positive found by Much's method, only three tubercle bacilli were found in the stained preparation.

DISCUSSION OF RESULTS

The tabulated findings show that the number of positive sputa found by both methods was the same. The number of bacilli exposed, as indicated by Gaffky's scale, was about ten per cent larger with the Schulte-Tigges method than with the Ziehl-Neelsen method.

The difference between our findings and those of Shoub may possibly be due to the use of fresh specimens by that author while our specimens were autoclaved in every case, thus securing uniform distribution and concentration of the microörganisms.

CONCLUSIONS

1. The Schulte-Tigges and Ziehl-Neelsen methods give the same number of positive specimens under the conditions obtaining in these laboratories.

2. Based on the Gaffky scale, the number of tubercle bacilli exposed is somewhat greater with the Schulte-Tigges than with the Ziehl-Neelsen method.

3. The Schulte-Tigges method is an apparently reliable staining procedure for tubercle bacilli. It might prove of practical value, particularly in laboratories where alcohol is difficult to obtain.

4. The Schulte-Tigges method does not have sufficient advantage over the Ziehl-Neelsen to warrant a change in the routine procedure used in these laboratories.

Thanks are due Miss Harriett Baker and Miss Lucile Roach for making many of the examinations.

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(1) SCHOUB: Jour. Bacteriol., 1923, viii, 121.
(2) SCHULTE-TIGGES: Deutsche med. Wchnschr., 1920, xlvi, 1225.

THE VALUE OF PERCUSSION IN THE DEMONSTRATION OF PULMONARY ANATOMIC CHANGES

PAUL M. ANDRUS[1]

Most illuminating has been the work of Bray (1) and of Heise (2) on the correlation of auscultatory chest findings with disease processes. The latter author has demonstrated a higher percentage of so called abnormal breath sounds over normal lungs than over those showing radiographic tuberculosis.

We have thought that a similar correlation of upper-lobe percussion findings with radiographic shadows might be equally instructive, having also regard to the types of pathological involvement.

Five hundred persons have been studied to this end, including a nontuberculous group of 26 per cent of the total. This latter in turn has included, as controls, a group of 38 clinically normal medical students. The nontuberculous class was composed, aside from the students, of patients reporting for investigation, either of nontuberculous chest conditions or as tuberculosis suspects, and finally adjudged nontuberculous.

The object of the study, as suggested in the title, has been to demonstrate the place of percussion, not as an agent in the diagnosis of disease, but as an indicator of anatomic changes in the underlying structures. It does not represent a personal opinion as to the value of percussion, but is rather a statistical study of the actual records as made by a well-trained sanatorium staff.

Recognizing the inherent difficulties of such a procedure, and the many sources of error that must inevitably creep in, we have still thought that the study might be useful in the demonstration of the value of percussion, "as it is done."

The following standards have been observed:

1. Individuals with intrapulmonary râles have been excluded. Râles, of course, guide us to the seat of disease, and might prejudice opinion as to percussion changes. Also, in the presence of râles, percussion changes become of secondary importance.

[1] Queen Alexandra Sanatorium, London, Ontario.

TABLE 1

Correlation of impairment and disease in individuals

	TUBERCULOUS 372		NON-TUBERCULOUS 128	
	Number	Per cent*	Number	Per cent
A. Individuals showing bilateral agreement:				
Impairment and disease right and left	51	13	2	1
No impairment or disease right and left	15	4	62	48
Impairment and disease right; no impairment or disease left	66	18	11	9
No impairment or disease right; impairment and disease left	13	4	1	1
Total showing bilateral agreement	145	39	76	59
B. Individuals showing unilateral agreement only:				
Disease and impairment right; disease and no impairment left	107	29	2	1
Disease and impairment right; impairment and no disease left	7	2	2	1
No impairment or disease right; disease and no impairment left	7	2	3	2
No impairment or disease right; impairment and no disease left	1		6	5
Total showing agreement right; disagreement left	122	33	13	10
Disease and impairment left; disease and no impairment right	10	3	0	0
Disease and impairment left; impairment and no disease right	17	4	0	0
No impairment or disease left; disease and no impairment right	4	1	4	3
No impairment or disease left; impairment and no disease right	26	7	23	18
Total showing agreement left; disagreement right	57	15	27	21
Total showing unilateral agreement only	179	48	40	31
C. Individuals showing bilateral disagreement:				
Disease and no impairment right and left	13	3	3	2
Impairment and no disease right and left	3	1	6	5
Impairment and no disease right; disease and no impairment left	30	8	3	2
Disease and no impairment right; impairment and no disease left	2	1	0	0
Total showing bilateral disagreement	48	13	12	10

* Percentages estimated to nearest cipher.

2. Changes confined to the extreme apices have not been included. Only those extending to the second anterior rib and spine of the scapula, or lower, have been considered.

3. A close correlation of extent of radiographic shadows and impairment has not been attempted. The former for the most part exceeded the latter.

4. Impairment has been for the most part of moderate degree. When recorded over the right upper lobe it was considered to be definitely beyond the normal limits of degree or extent. Thus, a slightly higher pitched note above the right second anterior rib and spine of the scapula was considered normal, and abnormal only if the rise in pitch was very definite or extended

TABLE 2

Distribution of impairment in diseased and clear lungs

	TUBERCULOUS: 372 INDIVIDUALS; 744 LUNGS		NON-TUBERCULOUS: 128 INDIVIDUALS; 256 LUNGS	
	Number	Per cent	Number	Per cent
A. Diseased right lungs	260		23	
Showed impairment	231	89	16	70
Showed no impairment	29	11	7	30
B. Diseased left lungs	248		16	
Showed impairment	96	38	3	19
Showed no impairment	152	62	13	81
C. Clear right lungs	112		105	
Showed impairment	76	68	31	30
Showed no impairment	36	32	74	70
D. Clear left lungs	124		112	
Showed impairment	13	10	14	13
Showed no impairment	111	90	98	87
E. Right lungs (total)	372		128	
Showed agreement	267	72	85	66
Showed disagreement	105	28	43	34
F. Left lungs (total)	372		128	
Showed agreement	202	54	96	75
Showed disagreement	170	46	32	25

lower than the above limits. The left first interspace has been considered abnormal if the percussion note were at all higher pitched than in the left second interspace.

5. Impairment changes, as recorded, are the net result of a reasonably close agreement among several observers skilled in thoracic investigation.

6. By radiographic disease (the term *disease* is used in the text), we have meant that the shadows as seen in stereoscopic films bear the usual characters

of, and are quite consistent with, clinical tuberculosis. Thus, some individuals in the nontuberculous group showed radiographic shadows having the usual characters of tuberculous disease. Presumably, in some of these the shadows actually were of tuberculous origin although the individuals had never been demonstrably ill. Similarly, in the tuberculosis group, some individuals failed to show upper-lobe radiographic shadows that would in themselves be interpreted as probably tuberculous. Uniform thickening of the bronchial tree without localized opacities has not been classed as disease, although some of these were proved to be tuberculous, and appear as tuberculous individuals with clear (radiographically) lungs.

Tables 1 and 2 indicate the correlation of disease and impairment, from the standpoint of individuals and of lungs respectively.

The more outstanding features indicated in tables 1 and 2, considering first, the tuberculosis group, would appear to be:

1. Total bilateral agreement as to the presence or absence of disease and impairment in only 39 per cent of tuberculous individuals.
2. A high percentage of impairment over diseased right lungs (89 per cent) which figure appears to lose somewhat in significance when compared with impairment in 68 per cent of clear right lungs in the same group.
3. A relatively low percentage of impairment over diseased left lungs (38 per cent).
4. An infrequency of impairment over clear left lungs (10 per cent) as compared with 68 per cent over clear right lungs.

Comparing these with the nontuberculous group, however, it is seen that in this series there is a definitely higher percentage of agreement as to the presence or absence of impairment and disease, both from the standpoint of individuals and of lungs. This difference in degree of agreement would appear to consist essentially (table 3) of a higher percentage of agreement as to the presence of impairment and disease in the tuberculous than in the nontuberculous group, but also in a still higher percentage of agreement as to the absence of impairment and disease in the nontuberculous group.

The only figure we have been able to find in the literature as a basis of comparison is that of Barnes (3) who records radiographic disease in 49 per cent of 310 lungs of tuberculous individuals (right and left) showing no impairment or râles. In the similar group from our own series (328 lungs right and left, of tuberculous individuals without impairment or râles) 55 per cent showed radiographic disease. These figures appear reasonably close.

CLINICAL APPLICATION

The statistics in tables 1 and 2 are presented from the standpoint of disease, and the correlation of impairment with disease.

To be of working value, the reverse order of procedure would seem necessary, namely, a knowledge of the frequency of disease in the presence and absence of impairment.

Table 3 is presented to this end, and although simply the converse of table 2 gives different percentage findings.

TABLE 3

Distribution of disease in relation to impairment

	TUBERCULOUS: 372 INDIVIDUALS; 744 LUNGS		NON-TUBERCULOUS: 128 INDIVIDUALS; 256 LUNGS	
	Number	Per cent	Number	Per cent
A. Impairment present:				
Right lungs diseased	231	75	16	34
Right lungs clear	76	25	31	66
Left lungs diseased	96	88	3	18
Left lungs clear	13	12	14	82
B. Impairment absent:				
Right lungs diseased	29	45	7	9
Right lungs clear	36	55	74	91
Left lungs diseased	152	59	13	12
Left lungs clear	111	41	98	88

Study of this and the previous tables would indicate the significance of the presence or absence of impairment as indicators of the presence or absence of underlying disease, to be as follows in order of value:

1. Impairment over left upper lung as evidence of disease.
2. Absence of impairment over right upper lung as evidence of absence of disease.
3. Impairment over right upper lung as evidence of disease.
4. Absence of impairment over left upper lung as evidence of absence of disease.

In dealing with unknowns, we must presumably accept the standards as appearing in tuberculous individuals.

TYPES OF PATHOLOGICAL CHANGES

Again it would be of interest to know what type of pathological change, if any, is most likely to be indicated by the presence of impairment. A study of this factor has been attempted as in table 4.

As might be expected there appears, to be some relation between the frequency of impairment and the amount of air-containing tissue. Thus, consolidation shows a higher percentage of impairment than the more

TABLE 4

Correlation of impairment with types of disease in tuberculous lungs

	TUBERCULOUS LUNGS 508	
	Number	Per cent
A. Consolidation (air containing tissue minimal)	155	
Right lung shows impairment	83	97
Right lung shows no impairment	2	3
Left lung shows impairment	35	50
Left lung shows no impairment	35	50
B. Scattered parenchymatous and mottling (considerable air containing tissue)	114	
Right lung shows impairment	51	91
Right lung shows no impairment	5	9
Left lung shows impairment	22	38
Left lung shows no impairment	36	62
C. Peribronchial	75	
Right lung shows impairment	26	82
Right lung shows no impairment	6	18
Left lung shows impairment	13	31
Left lung shows no impairment	30	69
D. Fibrosis predominant	164	
Right lung shows impairment	75	86
Right lung shows no impairment	12	14
Left lung shows impairment	25	32
Left lung shows no impairment	52	68

scattered types of parenchymatous lesions, while shadows interpreted as peribronchial tuberculosis and tuberculous fibrosis show still lower figures.

These figures do not, however, appear sufficiently characteristic to guide us to an estimate of the type of underlying pathological change.

STUDENT GROUP

The figures extracted from the student group have so closely approximated those from the complete nontuberculous group that there has been no apparent object in separating them.

This group (clinically normal in spite of the presence of radiographic shadows consistent with tuberculous pathological changes in 33 per cent) we have studied with a view to obtaining a clue as to the normal limits of degree and extent of percussion changes over right upper lungs. Inasmuch as this series was specially prepared for this work, we have taken occasion to correlate also the breath sound changes.

Thus, of the 38 clinically normal students all showed the percussion note higher over the right upper lung than on the left. In 25, or 66 per cent, this rise in pitch was very slight, and did not extend lower than

TABLE 5

Correlation of percussion and breath sound changes in clinical normals

	STUDENTS 38	
	Number	Per cent
A. Diseased right lungs:		
Impairment present; breath sounds normal	2	
breath sounds abnormal	1	
Impairment absent; breath sounds normal	2	
breath sounds abnormal	1	
Total normal breath sounds	4	66
Total abnormal breath sounds	2	33
B. Clear right lungs:		
Impairment present; breath sounds normal	8	
breath sounds abnormal	2	
Impairment absent; breath sounds normal	17	
breath sounds abnormal	5	
Total number of breath sounds normal	25	78
Total number of breath sounds abnormal	7	22
C. Summary of right lungs in clinical normals:		
Impairment present; breath sounds normal	10	77
breath sounds abnormal	3	23
Impairment absent; breath sounds normal	19	76
breath sounds abnormal	6	24

the second anterior rib and the spine of scapula. Of the remainder, 2 showed marked rise in pitch above the second anterior rib, 10 above the third anterior rib, and one to the fourth anterior rib, the latter two classes extending lower than the spine of the scapula posteriorly.

The breath-sound findings were as given in table 5. The only changes of note were those involving intensity and duration of expiration. Consequently, by abnormal breath sounds we have meant that expiration equalled or exceeded inspiration in intensity and duration.

From this it will be observed that abnormal breath sounds, as above described, occurred in from one-quarter to one-third of right lungs, whether clear or showing impairment or disease, and apparently independently of each other.

These figures are of course much too small to warrant the drawing of acceptable conclusions. They are prepared from clinically normal individuals and are therefore not necessarily applicable to tuberculosis suspects. Also, it must be remembered that they refer to right lungs only.

A further observation of physical findings showed 4 of the 13 having presumably abnormal right-lung percussion findings to have also definite retraction and respiratory lagging of the right. None of these showed underlying radiographic disease, and in three of the four the breath-sound cycle was considered to be within the normal limits Miller (4) has recently stated that "inspection of the chest has proved to be of more value than percussion, and ranges next in worth to auscultation."

DISCUSSION OF DISCREPANCIES

The reasons for the apparent discrepancies as portrayed are of interest.

Aside from the very obvious fallibility of individual judgment on percussion and X-ray interpretation and diagnosis, first and foremost would seem to be:

1. The normal right-apex phenomena and lack of clear-cut standards of normal. Certainly we are not in a position to say that a marked rise of percussion pitch over the right apex, or the same extending into more distal areas, is necessarily beyond the normal limits. Percussion changes may conceivably be created or unrecognized, by reason of comparing the two sides for standards. We have, of course, attempted to establish a "basic note of resonance" for the individual lung, as described by Byers (5).

2. Second in importance is probably the nature of the pathological change with which we are dealing. Presumably, the extent of distribution and characters of the infiltrative process, on the one hand, and of the remaining air-containing tissue, on the other, constitute a delicate and complicated balance impossible of clinical separation, but is the end-result of what we identify as impairment or otherwise.

3. Pleural thickening of such distribution or character as not to be identified by radiographs can undoubtedly be a cause of unexplained impairment, as may other extrapulmonary factors.

4. Complete absorption of tuberculous deposits is a clinical and experimental fact (6). Unexplained percussion, breath-sound or objective structural changes may perhaps, on occasion, have their origin in such previous infiltrative processes.

CONCLUSIONS

1. Percussion findings must be interpreted in terms of underlying pathological change with great caution, even when accompanied by structural or (other than râles) auscultatory changes.

2. The significance of percussion findings as indicators of underlying anatomic changes may be estimated in order of value as in the section on clinical applications.

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A STUDY OF THE REACTIONS RESULTING FROM THE INTRACUTANEOUS INJECTION OF TUBERCULOUS AND OTHER PATHOLOGICAL URINES[1]

GEORGE G. ORNSTEIN AND M. MAXIN STEINBACH

The dream of many investigators is to find a biological test which is not only specific but is also an index of the activity of tuberculosis. When Wildbolz reported his "auto-urine" reaction it was believed that such a test had been obtained. This author concentrated the urine of a tuberculosis patient to one-tenth of its original volume, after which 0.1 cc. of this concentrated urine was injected intracutaneously into the same patient. Unfortunately, not a few authors claim that this test is a nonspecific reaction caused by the irritating action of the urinary salts. One of us (1) has shown that the urine prepared after the method of Wildbolz produces skin reactions in both tuberculous and normal guinea pigs, that after the same urine is dialyzed in a fish-skin sac against running tap-water no reactions are produced in either the tuberculous or normal guinea pig, and that therefore the reaction is due to the irritating urinary salts. Many other investigators had previously formed similar conclusions from their work on human beings.

It was thought by Wildbolz (2) and others that the poisonous substances given off by the tubercle bacilli are eliminated through the blood-stream and the urine. If such substances could be demonstrated there would be no question as to the patient having active tuberculosis. The fact that the Wildbolz test, as carried out by other investigators (1) (3) (4) (5) (6) (7) (8), did not demonstrate such substances, is not conclusive evidence however that they are not present in the urine of the actively tuberculous. For example, Calmette (9) says

Some authors say that they have succeeded in demonstrating the presence of tuberculin in the urine of the tuberculous, either by inoculation into the tuberculous guinea pig (Rappin and Fortineau) or by the reaction of Bordet-Gengou using the urine as antigen (Marmorek, Bergeron, Robert Debré and

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Paraf). This last reaction may be positive in some rare cases where pyuria exists, but it is then the bacilli expelled in abundance which play the rôle of antigen, and not the tuberculin. It has been in no way demonstrated that the latter can be found in a free state in the urine, nor indeed in the blood of patients.

From the above one may readily see that, before proceeding with the isolation of tuberculin-like substances from the urine of the tuberculous, it must be proved that tuberculin may be excreted into the urine and also be isolated in high enough concentration to produce a skin reaction in an allergic person. This should be demonstrable in guinea pigs by testing for tuberculin in the blood-stream and the urine after inoculation.

In our work we first attempted to rid the urine of the irritating urinary salts. We thought that this could be accomplished by the adoption of Zinsser's method (10) of obtaining the nucleoproteins and the proteose fraction of the tubercle bacilli. This author has shown that the specific skin reaction produced by the tuberculoproteins is due to these two groups. They produce a reaction almost as intense as appears with old tuberculin. He precipitates the nucleoproteins and the proteose residue by adding ten volumes of 95 per cent alcohol, after ridding the solution of the albumins by means of heat and acetic acid. In treating O. T. in the same manner we found that it lost none of its ability to produce skin reactions.

The preparation of the urine was as follows:

The urine was filtered, titrated and brought to pH 6. It was then allowed to boil for three minutes. After being allowed to cool it was filtered through filter paper and the amount carefully noted. Ten volumes of 95 per cent alcohol were then added to the filtrate. A precipitate was formed which was thrown down by centrifugation. The supernatant fluid was discarded and the alcohol allowed to evaporate from the sediment. After the evaporation was complete, normal saline solution was added until the original amount was obtained. The urine was passed through moistened filter paper (to avoid loss), in order to remove some of the insoluble substances which are probably salts. This material constituted the urinary substance for the intracutaneous tests.

Female guinea pigs were used throughout the experiment. Fine glass capillary pipettes were used for catheterization and no difficulty was encountered. Both tuberculous and normal guinea pigs were injected intracutaneously in pairs; each either with 0.1 cc. of O. T. (diluted 1 to 10), or with 0.1 cc. of the urine of a normal guinea pig or 0.1 cc. of the proteose fraction of the urine of a normal guinea pig as prepared above. A skin reaction appeared at the site of the injection only when tuberculin was given to the tuberculous guinea pig. The urine and the proteose fraction of the urine of the normal guinea pig produced no skin reactions, as may be seen in table 1.

Two normal guinea pigs were then injected intraperitoneally with 1 cc. of O. T. The animals were bled from the heart and catheterized before the injection, and at intervals of 2,

6 and 24 hours afterward. The technique described above was used in the preparation of the urines. The blood was centrifugated and the supernatant serum pipetted off. The proteose fractions of the urines and the blood serums were injected into tuberculous and normal guinea pigs. The skin reactions were controlled by the injection of O. T. diluted 1 to 10. The volumetric unit for the intracutaneous injection was 0.1 cc.

The proteose fraction of the urine and the blood-serum that had been removed from the normal guinea pig 2 and 6 hours after the injection of tuberculin gave definite skin reactions when injected intracutaneously

TABLE 1

	INTRACUTANEOUS INJECTION OF 0.1 CC. OF O. T. (1–10)	INTRACUTANEOUS INJECTION OF 0.1 CC. OF NORMAL GUINEA PIG URINE	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF NORMAL GUINEA PIG URINE
Normal guinea pig	−	−	−
Tuberculous guinea pig	+	−	−

+ = skin reaction.
− = no skin reaction.

TABLE 2

	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE BEFORE INTRAPERITONEAL INJECTION OF O.T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE 2 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE 6 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE 24 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF TUBERCLE BACILLI
Normal guinea pig	−	−	−	−	−
Tuberculous guinea pig	−	+	+	−	+

+ = skin reaction.
− = no skin reaction.

into the tuberculous guinea pigs. The proteose fraction of the urine and the blood serum removed before and twenty-four hours after the injection of tuberculin gave no skin reactions when injected into tuberculous animals.

The skin reactions appeared about four hours after the intracutaneous injections, and reached their maximum intensity in twelve hours. After twenty-four hours they began to fade rapidly. Except for the more rapid appearance and disappearance, the reactions were difficult to distinguish from the one produced at the site of the injection of the

tuberculin in the same tuberculous guinea pig. The detailed results may be seen in tables 2 and 3.

The experiment was repeated and the same results were obtained.

The question then arose as to whether tuberculin could be demonstrated in the same manner in tuberculous guinea pigs. To this end a normal and a tuberculous guinea pig were each injected intraperitoneally with 1 cc. of O. T. The urine was collected after one and two hours. A collection was also attempted at the fourth and sixth hours, but the bladder was empty. The tuberculous guinea pig died during the night. The proteose fractions of the urines were injected intracutaneously into tuberculous and normal guinea pigs. The skin reactions were controlled by the injection of O. T. (1–10 dilution). The unit for the

TABLE 3

	INTRACUTANEOUS INJECTION OF 0.1 CC. OF SERUM OF NORMAL GUINEA PIG BEFORE INJECTION INTRAPERITONEALLY WITH O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF SERUM OF NORMAL GUINEA PIG 2 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF SERUM OF NORMAL GUINEA PIG 6 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF SERUM OF NORMAL GUINEA PIG 24 HOURS AFTER INTRAPERITONEAL INJECTION OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF O. T. (DILUTED 1-10)
Normal guinea pig..	−	−	−	−	−
Tuberculous guinea pig.....	−	+	+	−	+

+ = skin reaction.
− = no skin reaction.

intracutaneous injection was 0.1 cc. A skin reaction was obtained in the tuberculous guinea pig with the proteose fraction of the urine of the normal guinea pig two hours after the intraperitoneal injection of the 1 cc. of O. T. Similar reactions were produced by the proteose fraction of the urine of the tuberculous guinea pig one and two hours after intraperitoneal injection of 1 cc. of O. T. The skin reactions appeared about four hours after the intracutaneous injection had reached their maximum intensity in twelve hours and began to fade quickly after twenty-four hours. The reactions resembled the tuberculin reaction which was used as a control. The detailed results may be seen in table 4.

An attempt was then made to isolate similar substances from a tuberculous guinea pig. No skin reactions were produced by the intracutaneous injection of the proteose fraction of the urine of a tuberculous guinea

pig into a tuberculin-allergic one. A question of insufficient concentration of the tuberculin-like substances arose. The small quantity of urine collected from the guinea pig allowed little or no concentration. The blood-stream offered less difficulty as to concentration. A normal

TABLE 4

	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE OF A NORMAL GUINEA PIG 1 HOUR AFTER INJECTION INTRAPERITONEALLY OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE OF A NORMAL GUINEA PIG 2 HOURS AFTER INJECTION INTRAPERITONEALLY OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE OF A TUBERCULOUS GUINEA PIG 1 HOUR AFTER INJECTION INTRAPERITONEALLY OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION OF URINE OF A TUBERCULOUS GUINEA PIG 2 HOURS AFTER INJECTION INTRAPERITONEALLY OF 1 CC. OF O. T.	INTRACUTANEOUS INJECTION OF 0.1 CC. OF OLD TUBERCULIN DILUTED 1 TO 20
Normal guinea pig..	−	−	−	−	−
Tuberculous guinea pig.....	−	+	+	+	+

\+ = skin reaction.
− = no skin reaction.

TABLE 5

CASE	DIAGNOSIS	INTRACUTANEOUS INJECTION INTO TUBERCULOUS GUINEA PIG OF		INTRACUTANEOUS INJECTION INTO NORMAL GUINEA PIG OF	
		Proteose fraction of urine	Old Tuberculin diluted 1–10	Proteose fraction of urine	Old Tuberculin diluted 1–10
W. C.....	Pulmonary tuberculosis	−	+	−	−
D.....	Pulmonary tuberculosis	−	+	−	−
B.....	Pulmonary tuberculosis	−	+	−	−
G.....	Pulmonary tuberculosis	−	+	−	−
P. C.....	Pulmonary tuberculosis	−	+	−	−
W. C.....	Pulmonary tuberculosis	−	+	−	−
S. K.....	Pulmonary tuberculosis	−	+	−	−
K.....	Pulmonary tuberculosis	−	+	−	−
C.....	Pulmonary tuberculosis	−	+	−	−

\+ = skin reaction.
− = no skin reaction.

and a tuberculous guinea pig were bled to death from the heart. Ten cubic centimetres of the blood-serum of each was evaporated to dryness in a petri-dish by means of an electric fan. To the contents of each dish 1 cc. of normal saline solution was added. In this manner the serum was concentrated to one-tenth of its original volume, and 0.1 cc. of the

concentrated serum was used for intracutaneous test on a normal and a tuberculous guinea pig. No skin reactions were produced.

We next decided to work with the urine of actively tuberculous human beings, as the amount of urine obtainable from a guinea pig was too small to allow us to draw the conclusion that no tuberculin-like substances were present. The cases used had pulmonary tuberculosis in various stages from the slightly active to the very active. As a matter of convenience it was decided to use the morning specimen of urine. The hydrogen-ion concentration was tested and if alkaline was brought to pH 6. The urine was filtered through filter paper and the filtrate boiled for three minutes. The urine was again filtered to remove any albumin if present. To 10 cc. of the filtrate 10 volumes of 95 per cent alcohol were added (in order to precipitate the nucleoproteins and proteose group if they were present) and the whole solution centrifugated. The supernatant fluid was discarded and the sediment was not touched until the alcohol had completely evaporated. The sediment was then dissolved in 10 cc. of physiological salt solution. Insoluble substances precipitated by the alcohol were removed by filtering through filter paper. The filtrate was then used for the intracutaneous tests.

The intracutaneous injections were given to tuberculous guinea pigs with normal guinea pigs as controls. For controlling the skin reactions O. T. diluted 1 to 20 was injected intracutaneously. The unit for injection was 0.1 cc.

No skin reactions were noticed (table 5). Again the question of sufficient concentration of tuberculin-like substances arose. We decided to use a more concentrated urine. The technique was modified by using 25 cc. of urine instead of 10 cc. The sediment was suspended in 1 cc. of physiological salt solution. This procedure concentrated the urine to 1/25 of its original volume. Using this concentrated urine, reactions were obtained (table 6). As can be seen from the table the reactions were too varying to be of any value. The question then arose as to whether the morning specimen of urine was not the cause of the irregular results.

As a rule the tuberculous patient is afebrile in the morning hours, and perhaps the smallest amount of tuberculin-like substances may be excreted at this period. It was also decided to use human beings for the skin injections, inasmuch as the latter are more sensitive to tuberculin than guinea pigs and will react to smaller quantities of tuberculin-like substances than sensitive guinea pigs.

TABLE 6

CASE NUMBER	DATE	DIAGNOSIS	ACTIVITY	SPUTUM EXAMINATION	INTRACUTANEOUS INJECTION INTO TUBERCULOUS GUINEA PIG OF		INTRACUTANEOUS INJECTION INTO NORMAL GUINEA PIG OF	
					Proteose fraction of urine	Old Tuberculin diluted 1–10	Proteose fraction of urine	Old Tuberculin diluted 1–10
P. K.	1/20	Pulmonary tuberculosis	Active		+	+	–	–
P. K.	1/26	Pulmonary tuberculosis	Active		+	+	–	–
2102	1/30	Pulmonary tuberculosis	Active		–	+	–	–
2120	1/30	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	–	–
2178	1/31	Pulmonary tuberculosis		Tubercle bacilli not found	–	+	–	–
2178	2/7				+	+	–	–
2178	2/11				+	+	–	–
2516	2/9	Pulmonary tuberculosis	Active	Tubercle bacilli found	–	+	–	–
2516	2/11				–	+	–	–
2226	2/11	Pulmonary tuberculosis	Active	Tubercle bacilli found	–	+	–	–
2275	2/12	Pulmonary tuberculosis	Active	Tubercle bacilli found	–	+	–	–
2886	2/25	Pulmonary tuberculosis			+	+	–	–
1015	2/25	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	–	–
1015	2/26				–	+	–	–
1015	3/1				+	+	–	–
1015	3/2				+	+	–	–
1015	3/5				+	+	–	–
1015	3/6				–	+	–	–
1015	3/7				–	+	–	–
1015	3/8				–	+	–	–
2297	3/1	Pulmonary tuberculosis	Active	Tubercle bacilli found	–	+	–	–
2398	3/10	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	–	–
2398	3/13				+	+	–	–

2398	3/14				−	+	−	−
2398	3/15				−	+	−	−
2398	3/17				−	+	−	−
2545	3/22	Pulmonary tuberculosis	Active	Tubercle bacilli found	−	+	−	−
2419	3/27	Pulmonary tuberculosis	Inactive	Tubercle bacilli not found	−	+	−	−
2418	3/27	Pulmonary tuberculosis	Inactive	Tubercle bacilli not found	+	+	−	−
2463	3/28	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	−	−
2463	3/29				−	+	−	−
2463	3/30				−	+	−	−
2463	4/4				+	+	−	−
1405	4/7	Pulmonary tuberculosis	Inactive	Tubercle bacilli found	+	+	−	−
2522	4/10	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	−	−
2720	4/12	Neoplasm		Tubercle bacilli not found	+	+	−	−
2720	5/2	Neoplasm			−	+	−	−
2599	4/15	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	−	−
2599	4/17				−	+	−	−
2599	4/18				+	+	−	−
2520	4/15	Pulmonary tuberculosis	Active	Tubercle bacilli found	−	+	−	−
2553	4/23	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	−	−
2857	5/2	Pulmonary tuberculosis	Active	Tubercle bacilli found	+	+	−	−
2857	5/3				−	+	−	−
2857	5/4				−	+	−	−
2857	5/5				+	+	−	−
2857	5/7				+	+	−	−
2857	5/9				+	+	−	−
2857	5/12				−	+	−	−
2857	5/15				−	+	−	−

+ = skin reaction.
− = no skin reaction.

TABLE 7

NAME	DATE	DIAGNOSIS	ACTIVITY	SPUTUM	INTRACUTANEOUS INJECTION INTO THE PATIENT OF 0.1 CC. OF PROTEOSE FRACTION OF HIS OWN URINE	INTRACUTANEOUS INJECTION INTO SAME PATIENT OF 0.1 CC. O. T. DILUTED 1-100,000 FOR CONTROL	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION INTO ANOTHER TUBERCULOUS PATIENT	INTRACUTANEOUS INJECTION INTO SAME PATIENT OF 0.1 CC. O. T. DILUTED 1-100,000 FOR CONTROL
S. G.	8/18/23	Pulmonary tuberculosis	iiic	Positive	−	−		
I. K	8/21/23	Pulmonary tuberculosis	iiic	Positive	+	+		
R. L	8/21/23	Pulmonary tuberculosis	iiic	Positive	+	−		
F. G.	8/21/23	Pulmonary tuberculosis	iiic	Positive	+	+		
I. G.	8/23/23	Pulmonary tuberculosis	iiia	Positive	+	+		
S. M.	8/23/23	Pulmonary tuberculosis	iiic	Positive	−	−		
S. M.	8/28/23	Pulmonary tuberculosis	iiic	Positive	−	−		
I. W.	8/28/23	Pulmonary tuberculosis	iiic	Positive	+	+		
M. K.	8/28/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
H. A.	8/30/23	Pulmonary tuberculosis	iiic	Positive	+	+		
J. C.	9/ 5/23	Pulmonary tuberculosis	iiic	Positive	+	+		
S. D.	9/ 5/23	Pulmonary tuberculosis	iiic	Positive	+	+		
A. C.	9/ 6/23	Pulmonary tuberculosis	iiic	Positive	+	+		
M. B.	9/ 6/23	Pulmonary tuberculosis	iiic	Positive	+	+		
S. S.	9/ 6/23	Pulmonary tuberculosis	iiib	Positive	−	−		
J. L.	9/ 6/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
A. J.	9/ 7/23	Pulmonary tuberculosis	iiib	Positive	+	+	+	+
A. C.	9/ 8/23	Pulmonary tuberculosis	iiib	Positive	+	+	+	+
R. S.	9/11/23	Pulmonary tuberculosis	iic	Positive	+	+	+	+
S. A.	9/11/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
S. S.	9/14/23	Pulmonary tuberculosis	iia	Negative	+	+		

S. H.	9/15/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
H. R.	9/15/23	Pulmonary tuberculosis	iiib	Positive	+	+	+	+
M. J.	9/19/23	Pulmonary tuberculosis	iia	Positive	−	+	−	−
B. F	9/19/23	Pulmonary tuberculosis	iiic	Positive	−	−	+	+
R. D	9/22/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
J. B.	9/22/23	Pulmonary tuberculosis	iiia	Positive	−	+	−	−
R. N.	9/22/23	Pulmonary tuberculosis	iiia	Positive	−	−		
B. F.	9/26/23	Pulmonary tuberculosis	iiic	Positive	+	−	+	+
J. S.	9/26/23	Pulmonary tuberculosis	iiia	Positive	−	+		
J. G.	9/27/23	Pulmona y tuberculosis	iiic	Positive	+	−	+	+
B. T.	9/27/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	−
S. L.	9/28/23	Pulmonary tuberculosis	iiib	Negative	−	+		
J. G.	9/30/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+
A. K	9/30/23	Pulmonary tuberculosis	iiic	Positive	+	+	+	+

+ = skin reaction.
− = no skin reaction.
ii = moderate pulmonary tuberculosis.
iii = far advanced pulmonary tuberculosis.
a = inactive.
b = moderate activity.
c = very active.

The first group of patients complained of severe pain immediately after the intracutaneous injections of the proteose fraction of the urine of tuberculous human beings. An area of inflammation appeared at once which was painful and tender to the touch and remained for 72 hours, when it gradually faded.

We next attempted to eliminate the salts as a factor, by dialyzing the urine in fish-skin sacs against running tap-water. The urine was allowed to dialyze until the specific gravity was that of the tap-water. This generally took about five to six hours. The technique for the prepara-

TABLE 8

NAME	DATE	DIAGNOSIS	INTRACUTANEOUS INJECTION INTO PATIENT OF 0.1 CC. OF PROTEOSE FRACTION OF HIS OWN URINE	INTRACUTANEOUS INJECTION INTO SAME PATIENT OF 0.1 CC. O. T. DILUTED 1-100,000 FOR CONTROL	INTRACUTANEOUS INJECTION OF 0.1 CC. OF PROTEOSE FRACTION INTO ANOTHER PATIENT	INTRACUTANEOUS INJECTION INTO SAME PATIENT OF 0.1 CC. O. T. DILUTED 1-100,000 FOR CONTROL
G. O.	9/14/23	Normal	−	+	−	+
J. P.	9/14/23	Bronchiectasis	−	+		
E. Z.	9/22/23	Tumor of lung	+	+	+	+
C. P.	10/ 3/23	Cardionephritic	+	+	−	−
Y. L.	10/11/23	Cardionephritic	−	−		
F. S.	10/11/23	Cardionephritic	+	+		
I. G.	10/11/23	Bronchiectasis	−	−	+	+
J. P.	2/11/24	Pneumonia	−	+	+	−
R. S.	2/11/24	Pneumonia	+	+	+	−
P. R.	2/11/24	Cardionephritic	−	−	+	+
P. H.	2/11/24	Rheumatism	−	+	+	+
B. O.	2/11/24	Rheumatism	+	+	+	+
N. S.	2/11/24	Rheumatism	−	−	+	−

+ = skin reaction.
− = no skin reaction.

tion of the proteose fraction of the urine was carried out as in our previous experiments. There were no more painful reactions produced by the injection of the proteose fraction of the urine. An auto-urine injection was given intracutaneously, and a similar amount was injected into another tuberculous patient. The skin reactions were controlled by the intracutaneous injection of 0.1 cc. of 1 to 100,000 dilution of O. T. Reactions were constantly obtained with the proteose fraction of the urine of the active tuberculous patients.

There was no immediate reaction. An area of erythema with a centre

of induration appeared in 4 to 6 hours, reaching its peak in 8 hours and remaining so for 24 hours, when it started to fade. The reactions resembled the tuberculin skin reaction, appearing a little before and not lasting as long.

For purposes of control the proteose fractions of the urine of normal individuals and inactive cases of pulmonary tuberculosis were prepared and injected in like manner. No skin reactions were noted. However, the proteose fractions of the urine of other pathological conditions produce similar reactions to one seen after the intracutaneous injection of the proteose fraction of the urine of the actively tuberculous.

The details of the various intracutaneous tests may be seen in tables 7 and 8.

It is noteworthy that in the pathological conditions which we studied the proteose fraction of the urine on injection intracutaneously produced a skin reaction. The type of reaction produced was the same with all the pathological urines. The question then arises as to whether the same substance is eliminated in the urine in all diseases. If we were to judge the substance by the reactions produced, we could say that the proteose fraction was the same in all pathological conditions. The intensity of the reaction was in direct proportion to the activity of the disease. The sensitiveness of the skin also played a part in the reaction. In morbid conditions no skin reactions were obtained, whereas if the material was injected into a sensitive skin a severe reaction occurred.

CONCLUSIONS

1. Tuberculin injected into a normal or tuberculous guinea pig is excreted through the blood-stream and the urine without impairing its ability to produce specific skin reactions when injected into other tuberculous animals. The tuberculin is excreted more rapidly in the tuberculous animal.

2. Tuberculin-like substances are not recovered from the urine or blood-stream of tuberculous guinea pigs.

3. No skin reactions are produced by the intracutaneous injection of the proteose fraction of the urine of the normal human being and of inactive cases of pulmonary tuberculosis.

4. The skin reactions produced by the intracutaneous injection of the proteose fraction of the urine of the actively tuberculous do not differ from those produced by the injections of the proteose fraction of the urines of some other pathological conditions.

5. In the above work we have not been able to be certain of the presence of true tuberculin in the urine of the actively tuberculous. The proteose fraction of urines from the pathological conditions studied by us, as well as the proteose fraction from tuberculous conditions, produce similar skin reactions in both tuberculous and nontuberculous individuals. We must therefore conclude that these reactions are nonspecific and are of no diagnostic value. They would seem to be due to some nonspecific hypersensitiveness of the skin in the reacting patient.

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STUDIES IN TUBERCULOSIS IMMUNITY

I. DIAGNOSTIC AND SENSITIZING PROPERTIES OF SOME NEW DERIVATIVES OF TUBERCULIN[1,2,3]

FREDERICK C. EBERSON

The phenomenon of skin hypersensitiveness to tuberculin has led to an inordinate amount of conflicting comment on the subject during the past two decades. The possibility of extending the observations to problems of tuberculosis immunity and therapy was soon recognized, and the result has been a voluminous literature on such much-mooted questions as the nature of the tuberculin reaction, its specificity and the chemical constitution of tuberculins in general.

The present study, preliminary to a series of separate investigations of certain obscure phases in tuberculosis immunology, is an attempt to obtain a modified tuberculin derivative or principle which may be more useful than current preparations in the early diagnosis of tuberculosis, particularly in connection with a wider range of specificity for the bovine type of tubercle bacillus. As a corollary to this, the mechanism and probable nature of the reaction will lend itself to a tentative interpretation.

The diagnostic significance of the cutaneous bovine tuberculin reaction has been studied within recent years, and the conclusions drawn by different investigators are at variance. Synwoldt (1), Bernheim-Karrer (2), and others have reported discrepant observations on the use of bovine and human tuberculin clinically and in experimental animals. A recognized difficulty in attacking the problem is at once apparent from our lack of a definite standardized product of known composition. To obviate this difficulty the tuberculin must be prepared from bacilli grown under special conditions, free from complex

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[2] This work was made possible by a grant from the Hennepin County Tuberculosis Association in Minneapolis during the tenure of a Graduate Fellowship in Tuberculosis Research supported by that organization.

[3] A preliminary report of this work is published in the *Proceedings of the Society for Experimental Biology and Medicine*, May 8, 1924, xxi, 539.

substances that are present in the culture media which are ordinarily used. Such a protein-free substrate would seem to be an ideal starting-point for the isolation of active principles that may be present in tuberculin. With this in mind, the modified derivatives on which the present study is based are being investigated further and evaluated.

LOCAL TUBERCULIN HYPERSENSITIVENESS FROM THE BIOLOGICAL STANDPOINT

Susceptibility to tuberculin has been regarded quite generally as an expression of a protective mechanism toward infection with tuberculosis, at least in the sense that a definite skin reaction is correlated with a certain amount of resistance in the individual. Attesting to this idea is the well-known fact that in tuberculous persons systemic and local reactions to tuberculin are inversely correlated with the severity and extent of infection already present. Tuberculin sensitivity, therefore, appears to be a function of tuberculous tissues and is manifested as a local reaction when union is established between these and tuberculin. So Bessau (3) would interpret the reaction. There is abundant evidence at hand to show that the local response to tuberculin is an expression of the individual's capacity to form tuberculous tissues through the action of stimulating or "irritating" substances in tuberculin. It is suggested, therefore, that the reaction is solely between the latter and the newly developed tuberculous tissue. A similar view had been expressed by Baldwin (4) some years ago. In this connection we have further evidence of another kind from the studies of those who are attempting to relate tuberculin hypersensitiveness to anaphylaxis. Rondoni (5), for example, in observing the action of tuberculin on the isolated guinea-pig heart, found that both normal and tuberculous animals behaved exactly alike, provided the hearts from tuberculous guinea pigs were free from lesions. To what extent this viewpoint squares with the theory of antibody formation remains to be seen. Certainly, according to many observers, including Bessau, the histological picture of characteristic tissue changes induced by local tuberculin injections does not seem to have any counterpart in the theory. Furthermore, it is argued that, contrary to antibody phenomena, a local inflammatory reaction occurs with each new addition of tuberculin to any area of local tuberculin response. The question may be dismissed at this point, for the present, in noting that opinion is divided concerning the antigen-antibody nature of tuberculin reactions. Recently, Selter (6) has offered

as proof against such a viewpoint the following considerations: Substances of an antibody nature cannot be demonstrated in the tuberculous body; treatment with sublethal doses of tuberculin confers no protection against fatal doses in tuberculous animals; susceptibility to tuberculin cannot be transferred passively; no evidence exists to show that tuberculin is antigenic or capable of immunizing activity. These conclusions are of particular interest in connection with our experimental findings and will be discussed later.

It is important, at all events, to try to adduce possible reasons for the failure of tuberculin to produce susceptibility in the sense of a true antibody phenomenon, such as Pirquet has taught. The seeming failure up to the present time need not, however, discredit the antigen-antibody theory. The difficulty may well be due to technical procedures and to factors related to absorption and dissemination of the material which has been studied. Pharmacological principles have given abundant evidence of the important rôle played by solubility, diffusibility and penetration of substances that are used in local and general therapy. These fundamental principles are the same for any biological reaction between tissues and the substances injected, be these drugs, tuberculins or proteins in general. From Baldwin, Bessau and Selter we learn that killed tubercle bacilli or their products, when absorbed with relative difficulty, are capable of producing local tuberculin hypersensitiveness. From this point we come by easy stages to an analysis of the mechanism of tuberculin reactions which will be discussed in its proper place.

ANTIGENS WITH KNOWN CONSTITUTION OF SPECIFIC GROUPS

That there is a relation between serological specificity and chemical structure of antigens is within the realm of established fact. The chemistry of different microörganisms and related phases of this vast problem are outside the scope of this investigation and cannot be taken up here. Of special value and interest from our standpoint, however, are the numerous studies of Landsteiner and his collaborators (7) (8) (9) (10) (11) (12) (13) (14) whose investigations gave impetus to our present study. In brief, the introduction of various groups such as *acetyl*, *diazo*, *methyl*, *nitro*, and many others into proteins, produced antigens that could be differentiated by serological methods. It was found that species specificity could be altered while effecting new structural specificity. In certain instances the latter, though most pro-

nounced, was accompanied by a slight degree of species specificity. An application of this principle to tuberculin and to the products of tubercle bacilli suggested itself, and coincided with our own ideas concerning antigens in general which were published several years ago (15).

The point of departure in our experiments centered on the properties of modified antigens and the possibility of extending the range of specificity through certain chemical alterations of the protein or nonprotein substances in tuberculin. The results which have been obtained appear to be consistent and in keeping with the biological, pharmacological and immunological principles which are probably involved in the mechanism.

We believe that the specific substance which produces a local tuberculin susceptibility is present in both the tubercle bacillus and in tuberculin and is the same substance in either case. Accordingly, it was of interest to prepare some derivatives of tuberculin and to study these products under the following headings:

(a) Potency of tuberculin derivatives as compared with untreated whole tuberculin.

(b) Diagnostic value of tuberculin derivatives in very early stages of experimental tuberculosis.

(c) Range of specificity of tuberculin derivatives for homologous and heterologous types of tubercle infection.

(d) Sensitizing properties of tuberculin derivatives.

(e) Active immunization with tuberculin derivatives.

(f) Therapeutic value of tuberculin derivatives in early and advanced stages of experimental tuberculosis.

The present report will be confined to the first four items, pending extensive experimental work which is in progress, especially in connection with the immunization and therapeutic aspects of our general problem. Under the same headings, clinical studies are being made also, and these, with certain exceptions, will be reported at a later date.

EXPERIMENTAL

Preparation of Tuberculin Derivatives

Derivatives were prepared from human and bovine tuberculin (Koch's O.T.) and tested for potency against human and bovine tubercle infection in guinea pigs. In a subsequent report the results which were obtained with bovine tuberculin derivatives will be described in con-

nection with the problem of cross-sensitization. In the experiments now under consideration three preparations were used and studied in relation to experimental infection with a human and bovine strain of tubercle bacilli.

1. Acetyl Derivative

Tuberculin was added gradually to pure methyl alcohol in the proportion of one to ten. The heavy flocculent precipitate was filtered by suction and washed with absolute alcohol, then ether. To the precipitate, still moist with ether, equal parts of acetic anhydride and benzoyl (50 cc. of each) were added in a flask, and next heated in a reflux condenser for 4 hours on a steam-bath. To prevent absorption of atmospheric moisture a calcium-chloride tube was attached to the condenser. The precipitate, after decantation of the supernatant fluid, was washed repeatedly with and suspended in 95 per cent ethyl alcohol for 6 to 8 hours. It was re-suspended for 4 to 6 hours in distilled water made slightly alkaline with 20 per cent sodium bicarbonate, washed once with distilled water and alcohol, and thoroughly ground in a mortar with the gradual addition of equal parts of pure glycerine and physiological salt solution. It was found that a stable and finely divided emulsion could be prepared by adding the glycerine in small quantities prior to the salt solution. The final volume was made up to one and one-half times that of the original tuberculin, neutralized (if necessary), and preserved with 0.25 per cent tricresol.

2. Benzoyl Derivative

Tuberculin was added to ten volumes of pure methyl alcohol by gradual addition, and the precipitate dissolved in one and one-half volumes of sterile distilled water. Four cubic centimetres of benzoyl chloride were added drop by drop to the solution in a separatory funnel in the presence of an excess of 20 per cent sodium bicarbonate, and the mixture was shaken thoroughly between additions. Throughout the procedure a slightly alkaline reaction was maintained and the mixture allowed to stand several hours before filtering. The precipitate, after drying at room temperature (20–24°C.), was washed with 95 per cent ethyl alcohol, absolute alcohol, then ether, and suspended in numerous fresh changes of ether before filtering again. Repeated washings on the filter paper were continued until the ether was free from benzoic acid. The precipitate was finally ground in a mortar, with addition

of glycerine and physiological salt solution, and brought up to a volume of one and one-fifth times that of the original tuberculin used. Tricresol was added to make a concentration of 0.25 per cent.

3. Ether-Insoluble "X"

To the filtrate, which was obtained after precipitation of tuberculin in 25 volumes of methyl alcohol, two to three volumes of ether were added. The resulting light brown precipitate was dissolved in physiological salt solution made up to two-thirds of the original volume of tuberculin and preserved with 0.25 per cent tricresol. These alcoholic filtrates, when concentrated at a temperature of 20 to 25°C, for four weeks, yielded a gummy, brown residue which was soluble in water, insoluble in alcohol, and was precipitated by tannic and picric acids and mercuric chloride. Negative reactions were obtained with iodin-potassium-iodide, mercuric-potassium-iodide, biuret, Millon, xanthoproteic and Liebermann tests. The Lassaigne test for nitrogen was positive.

Cutaneous Tests with Tuberculin Derivatives

Potency of the tuberculin derivatives was first determined by comparing with untreated whole tuberculin the reactions which were obtained by intracutaneous injections at a stated interval after inoculation of guinea pigs with a strain of tubercle bacilli.

Guinea pigs weighing from 250 to 450 gm. were inoculated subcutaneously with a weighed amount of tubercle bacilli, which had been grown from four to five weeks on glycerine-bouillon. The culture was dried between filter papers to remove excess moisture and the bacilli weighed and ground in a porcelain mortar. A uniform suspension was thus prepared in physiological salt solution containing 0.4 mgm. of tubercle bacilli per cubic centimetre.

Intracutaneous injections were made with an all-glass Luer tuberculin syringe fitted with a 24-gauge needle, one-half inch long. The skin over the abdomen was clipped and shaved cleanly and cleansed with alcohol. Injections were placed several centimetres apart. The material for injection was measured accurately in each test, and ranged from 0.01 to 0.05 cc. of untreated old tuberculin and from 0.02 to 0.1 cc. of the derivatives other than the *ether-insoluble "X"* which was given in uniform quantities of 0.02 cc. Reactions were considered accord-

ing to the criteria of local infiltration, erythema, wheal-formation, induration of the inflammatory area and subsequent breaking-down and central necrosis of the lesion with scar-formation and pigmentation. A reaction of this type was regarded as very severe and recorded as four plus. Gradations were designated as three, two, one plus and plus-minus. Transitory reactions which faded after 24 hours and left no definite changes as above were considered questionable. All definitely positive reactions persisted over a period of several days to more than one week. Four plus reactions, in addition, were at least one by one centimetre in extent.

TABLE 1

GUINEA PIG	TUBERCLE BACILLUS STRAIN	TEST AFTER	O. T.		BENZOYL DERIVATIVE		ACETYL DERIVATIVE		DURATION OF REACTION AND DEGREE
			cc. injected	Result	cc. injected	Result	cc. injected	Result	
		days							
1	Human	11	0.05	Pos.			0.1	Pos.	O.T., 5 days, +++; derivative, 10 days, ++++
2	Human	18	0.05	Pos.	0.05	Pos.			O.T., 7 days, +++; derivative, 9 days, ++++
3	Bovine	11	0.05	Neg.			0.1	Pos.	O.T., negative; derivative, 10 days, +++
4	Bovine	18	0.05	?	0.05	Pos.			O.T., 2 days, questionable; derivative, 6 days, ++++
5	Uninoculated control		0.05	Neg.	0.05	Neg.	0.01	Neg.	
6	Uninoculated control		0.05	Neg.	0.05	Neg.	0.01	Neg.	

1. Animal Experiments

Series of guinea pigs were inoculated, respectively, with human and bovine tubercle bacilli (subcutaneous 0.4 mgm.). Intracutaneous tests were made 11 and 18 days after inoculation. The results are summarized in table 1, and are typical of several experiments.

From the foregoing experiments it follows that the tuberculin derivatives are potent and unimpaired by the treatment, and are capable of eliciting typical skin reactions in tuberculous guinea pigs. Of interest

was the observation that whole, untreated tuberculin failed to give as marked or as protracted a reaction as that elicited by the acetylated and benzoylated preparations. Especially significant is the fact that these derivatives gave pronounced skin reactions in animals which had been inoculated with bovine tubercle bacilli. The size of the lesions produced in the homologous and heterologous tubercle infection ranged from 0.5 x 0.75 cm. to 2 x 1 cm. Characteristic of these reactions was the formation of a central grayish-white zone which was surrounded by a diffusely reddened and indurated border. After 72 to 96 hours the site of injection showed crateriform pitting, and later crusting, which retrogressed at the end of 6 to 10 days, leaving residual scarring and pigmentation. In this series the animals survived infection for periods of 22 to 36 days with the bovine strain of tubercle bacilli, and 45 to 49 days with the human strain. Autopsy findings were typical, and showed a generalized tuberculosis with marked general adenopathy with the bovine type; guinea pigs infected with the human strain showed more lung involvement and no marked lymph-node changes.

2. Human Tuberculosis

A small series of tuberculosis patients was studied in an attempt to confirm the results which were obtained in experimentally infected guinea pigs. The clinical data must be deferred for the present. Five adult male patients were included in this preliminary study.

Summary of Clinical Study with Derivatives of Old Tuberculin

Case 1: Patient gave positive Pirquet test. X-ray findings in chest negative. Average temperature range for one week prior to the experiment, 97.0° to 98.6°.

March 10: Pirquet test positive.

March 12: 1:00 P.M., injected intracutaneously 0.01 cc. acetyl derivative and 0.01 benzoylated derivative of old tuberculin on forearm at points 6 cm. apart.

	Temperature	*Pulse*	*Remarks*
2:00 P.M.	98.8	96	
4:00 "	99.6	88	
6:00 "	99.4	116	
6:30 "	Slight chill		
8:00 "	101.6	110	
March 13: 6:00 A.M.	96.2	108	Refused nourishment; is quite weak; profuse sweating all morning; local reactions slight.
8:00 "	97.0	106	
10:00 "	96.2	86	

	12:00 M.	96.2	84	
	4:00 P.M.	97.2	80	
March 14:	8:00 A.M.	98.6	88	Brighter; feels better.
	4:00 P.M.	97.8	76	
March 15:	8:00 A.M.	95.8	88	Acetyl reaction 1.0 x 0.5 cm. Benzoyl reaction
	4:00 P.M.	97.8	80	2.5 x 1.0 cm. Appetite improved.

March 18: Skin reactions still definitely positive. Intense reddening, induration and wheal-formation. Size of areas reduced somewhat.

Case 2: Average temperature range for four days prior to experiment 96.8° to 98.0°. Patient had clinical picture and findings of tuberculous peritonitis.

March 12: 1:00 P.M., injected intracutaneously 0.01 cc. each of acetyl and benzoylated derivatives of old tuberculin on forearm at points 6 cm. apart.

		Temperature	*Pulse*	*Remarks*
	2:00 P.M.	98.2	102	
	4:00 "	98.4	104	
	6:00 "	97.2	104	Slight chill.
	8:00 "	96.2	108	
	10:00 "	104.6	120	
March 13:	4:00 A.M.	101.4	144	Complained of pain over entire body; refused
	6:00 "	101.4	136	all nourishment.
	8:00 "	99.6	134	
	12:00 M.	100.2	118	Local reactions slight; size of wheals about 1.0
	4:00 P.M.	99.6	118	x 1.0 cm. with marked erythema.
	8:00 "	99.4	120	
March 14:	9:00 A.M.	98.4	90	Feels better, takes nourishment.
	8:00 P.M.	97.2	100	
March 15:	8:00 A.M.	96.0	100	Local reactions unchanged.
	4:00 P.M	97.2	100	

For the succeeding week the temperature range was from 96.8° to 98.4° and the pulse rate from 80 to 108. The skin reactions were faded and showed residual pigmentation at the end of the second week.

These two patients illustrate the systemic and generalized reactions which followed intracutaneous injections of minute amounts of derivatives of tuberculin. The local reactions were definite but not very marked.

In the next series of patients, three in number, the picture was quite different. Here the local reactions were very pronounced and unusually severe, while the general reaction was negligible or absent. This group included two cases of advanced tuberculosis with definite pulmonary

findings and another in which the only definite sign was hemoptysis, although X-ray findings were negative.

Case 3: Advanced bilateral pulmonary tuberculosis. Average temperature and pulse for one week preceding experiment were, respectively, 98°–99° and 68–70.

March 12: 1:00 P.M., injected intracutaneously 0.01 cc. each of acetyl and benzoylated derivatives of old tuberculin on forearm at points several centimetres apart.

	Temperature	*Pulse*	*Remarks*
2:00 P.M.	97.8	64	
4:00 "	98.4	56	
6:00 "	98.8	72	
8:00 "	98.6	60	
10:00 "	98.6	64	
March 13: 6:00 A.M.	101.0	80	Marked local reactions. Infiltration and reddening are intense. Size of lesions 2.0 x 1.0 cm. each.
8:00 "	101.6	88	
10:00 "	100.8	80	
12:00 M.	100.4	80	
4:00 P.M.	98.6	80	
March 14: 8:00 A.M.	97.2	60	
4:00 P.M.	96.8	72	
March 15: 8:00 A.M.	97.8	68	Local reactions more pronounced. The lesions are 2.0 x 2.0 cm. each.
4:00 P.M.	98.6	60	

March 16–23: Temperature and pulse remained within the range of normal. The local areas of reaction were definitely positive for the week, but faded very gradually and left slight scars and pigmentation.

Case 4: Hemoptysis at intervals. Average temperature and pulse for the week preceding experiment were, respectively, 98.0° and 72.

March 12: 2:00 P.M. Intracutaneous injections as in the previous cases.

	Temperature	*Pulse*	*Remarks*
3:00 P.M.	98.0	68	
4:00 "	97.8	76	Slight headache.
6:00 "	98.0	72	Local reactions 1.5 x 1.0 cm.
8:00 "	97.8	74	
March 13: 4:00 A.M.	97.0	84	Local reactions more pronounced. Axillary glands swollen and painful.
6.00 "	99.4	100	
8:00 "	99.6	108	
10:00 "	100.2	88	
12:00 M.	99.2	84	
4:00 P.M.	100.2	94	Chills, headache.
8:00 "	100.4	84	Refused nourishment.

March 14:	8:00 A.M.	98.0	96	Headache; soreness in arm.
	4:00 P.M.	99.4	80	Lymphangitis present.

March 15: Temperature and pulse range same as that preceding intracutaneous test. Local reactions more intense on this date. Site of benzoylated derivative 2.0 x 2.0 cm., and that of acetyl derivative 1.0 x 0.5 cm. Infiltration, erythema and wheal-formation definite.

March 19: Local reactions fainter, and residual scarring and pigmentation with some induration at the sites of injection.

This patient was transferred to a sanatorium shortly afterward and proved to be definitely tuberculous.

Case 5: Advanced pulmonary tuberculosis. The temperature range for one week prior to experiment was 98.0° to 99.0° and the pulse 60 to 72. The condition of the patient was very poor.

March 12: 2:30 P.M. Intracutaneous injections as in the preceding.

	Temperature	*Pulse*	*Remarks*
4:00 P.M.	98.4	58	
6:00 "	98.6	48	
8:00 "	98.4	48	
12:00 M.	98.4	60	
March 13: 4:00 A.M.	98.0	52	
6:00 "	98.2	52	
8:00 "	98.6	64	
10:00 "	98.2	60	Local reactions 1.0 x 1.0 cm.
12:00 M.	99.2	48	Appetite poor.
4:00 P.M.	99.0	64	
March 14: 8:00 A.M	99.4	70	
4:00 P.M.	99.2	80	
March 15: 8:00 A.M.	98.0	52	Site of benzoylated derivative 2.0 x 2.0 cm., and
4:00 P.M.	98.0	52	acetyl derivative 0.5 x 0.5 cm.

March 18: Local reactions still present and less pronounced. Infiltration and erythema positive, and considerable pigmentation.

Evidence has been adduced in the preceding experiments to show that the tuberculin derivatives which have been studied are capable of eliciting in tuberculous animals and human beings typical skin reactions varying in intensity with the degree of infection present. In this respect the response to these substances follows the general rule which holds for tuberculin reactions. That these derivatives retain at least the original potency of tuberculin is apparent, and the rigorous chemi-

cal treatment which they have received is in no wise a deterrent to the specific reactions which they evoke. It has been shown also that these derivatives are more sensitive and have a wider range of specificity in the experimentally infected animal.

Having established the potency of these materials we proceed now to our study of their sensitizing properties, diagnostic value in different stages of tuberculosis, and the range of activity for homologous and heterologous types of tubercle-bacillus infection.

Diagnostic Range of Tuberculin Derivatives in Experimental Bovine and Human Tuberculosis

In the experimental animal we have an accurate method for determining the range of activity of tuberculin preparations. By using a fixed dose of bacilli for inoculation and a definite quantity of the test material for diagnostic skin reactions, we should be able to determine the range of specificity of our products. Clinically, there is abundant evidence to show that children react usually to both human and bovine tuberculin with the Pirquet technique. At times either one or the other or both may be negative. Again, the intracutaneous method, or Mantoux technique, has been found to be positive in all cases in which scarification gives a reaction.

Of interest for our study is the question of negative skin tests with the use of tuberculin in the presence of infection with a heterologous strain of tubercle bacilli, and in certain cases which give no reaction to human and bovine tuberculins regardless of the technique used. To this end we have studied the diagnostic value of tuberculin derivatives in human and bovine types of tuberculosis in guinea pigs and in a series of young patients. The latter group will be considered in a separate clinical report.

If the range of specificity can be extended by the methods which we have described, we should be able to diagnose bovine or human tubercle infection which otherwise would remain unrecognized in the early stages. Accordingly, experiments were devised to investigate this point and it was found that the acetyl and benzoyl tuberculin derivatives and the *ether-insoluble* "*X*" give definite reactions with human as well as with bovine tubercle infections, notwithstanding the fact that the tuberculin was prepared from human strains of tubercle bacilli. The reactions were uniformly more intense and striking in experimental bovine infections.

Technique: Guinea pigs were inoculated subcutaneously with 0.4 mgm. of bovine or human tubercle bacilli and tested by the intracutaneous method at intervals after the initial infection.

Series A: Benzoyl and acetyl derivatives were injected intracutaneously in amounts of 0.1 cc. ten days after inoculation. Eight guinea pigs which were used in this series gave uniformly positive reactions. Three days after the appearance of skin reactions, 0.05 cc. of human O.T. was injected intracutaneously. In all instances the O.T. failed to elicit a local reaction. The following summary is typical of several experiments:

Guinea pig 1: Inoculated with human tubercle bacilli and tested with benzoyl human tuberculin derivative. Twenty-four hours later, at site of injection, an area 1.5 x 1 cm. with induration, local heat, swelling and marked erythema. Central part of lesion grayish-white and firm. Next day, infiltration more pronounced and reaction in general more intense. On tenth day, reaction had faded and left residual scarring with some pigmentation. In the interval, central necrosis and crusting had supervened, with progressively deepening umbilication which was observed in all of the experiments.

Guinea pig 2: Inoculated with bovine strain of tubercle bacilli and tested with benzoyl derivative. After 24 hours, reaction slight, and reached maximum in 48 hours. There was markedly reddened areola surrounding central flattened white zone. Induration marked, and area, 1 x 0.75 cm., intensely inflamed. Reaction still positive at end of eighth day, although animal was greatly emaciated and in poor condition. Before death, which occurred 32 days after initial infection, the central zone had sloughed away and become crusted over.

Guinea pig 3: Inoculated with human tubercle bacilli and tested with acetyl tuberculin derivative. After 24 hours, well-localized, markedly infiltrated area, 1 x 0.75 cm., with swelling and intense reddening which increased on succeeding day. As in preceding experiments, central white zone, 0.5 cm. in diameter. After 10 days, umbilication and crusting were present, and induration was slight.

Guinea pig 4: Inoculated with bovine tubercle bacilli and tested with acetyl derivative. Twenty-four hours after intracutaneous injection of latter, diffusely reddened and indurated area, 2 x 1 cm., with central white zone of 0.5 cm. On following day, induration, infiltration and edema more pronounced. The reaction persisted 12 days and terminated with central necrosis and crusting of the lesion.

The absence of a local reaction to intracutaneous injection of O.T. at a time when positive skin tests can be elicited with the derivatives speaks for the possibility that an immunizing action may have supplanted the initial hypersensitiveness. In other experiments it has been shown that typical skin reactions can be producted with O.T. and its derivatives when these are injected simultaneously. The significance of this observation will become more apparent in connection with the experiments on sensitization in which uninoculated guinea pigs were used.

Series B: Twelve guinea pigs were inoculated with 0.4 mgm. of tuber-

TABLE 2

GUINEA PIG	TUBERCLE BACILLUS STRAIN	SKIN TEST AFTER	MAXIMUM REACTION	DURATION OF REACTION	SIZE OF LESION	INTENSITY OF REACTION	
						Benzoyl	Acetyl
		days	*days*	*days*	*cm.*		
1	Human	3	3	Acetyl, 7 Benzoyl, 8	Acetyl, 0.5 x 0.5 Benzoyl, 0.5 x 0.5	+++	++++
2	Human	3	2	Acetyl, 6 Benzoyl, 7	Acetyl, 0.5 x 0.5 Benzoyl, 0.75 x 0.75	+++	++
3	Human	5	3	Acetyl, 6 Benzoyl, 8	Acetyl, 0.5 x 0.5 Benzoyl, 0.5 x 0.5	++	+
4	Human	5	2	Acetyl, 7 Benzoyl, 7	Acetyl, 0.25 x 0.25 Benzoyl, 0.25 x 0.25	+	+
5	Human	7	2	Acetyl, 8 Benzoyl, 8	Acetyl, 1.0 x 1.0 Benzoyl, 1.0 x 0.75	+++	+++
6	Human	7	1	Acetyl, 4 Benzoyl, 4	Acetyl, 0.5 x 0.5 Benzoyl, 1.0 x 1.0	++++	+++
7	Bovine	3	2	Acetyl, 4 Benzoyl, 4	Acetyl, 0.5 x 0.5 Benzoyl, 0.25 x 0.25	±	++
8	Bovine	3	2	Acetyl, 8 Benzoyl, 10	Acetyl, 0.25 x 0.25 Benzoyl, 0.25 x 0.25	+	+
9	Bovine	5	3	Acetyl, 6 Benzoyl, 6	Acetyl, 0.25 x 0.25 Benzoyl, 0.25 x 0.25	+	+
10	Bovine	5	2	Acetyl, 6 Benzoyl, 7	Acetyl, 0.25 x 0.25 Benzoyl, 0.5 x 0.5	+++	+++
11	Bovine	7	1	Acetyl, 8 Benzoyl, 8	Acetyl, 2.0 x 1.0 Benzoyl, 1.0 x 1.0	++++	++++
12	Bovine	7	2	Acetyl, 6 Benzoyl, 6	Acetyl, 0.5 x 0.5 Benzoyl, 1.0 x 1.0	++++	++
13, 14, 15, 16	Uninoculated controls: Acetyl, benzoyl derivatives and O.T. negative						

cle bacilli. Half of this group received the bovine strain and the remainder the human strain. At intervals of 3, 5 and 7 days after infection, a pair of animals were injected intracutaneously with 0.02 cc. each of the acetyl and benzoyl derivatives and untreated human O.T.

In none of these experiments was a positive reaction elicited with O.T., and uninoculated control animals gave negative results with the same preparations. The results are summarized in table 2.

From this experiment we may conclude that the acetyl and benzoyl derivatives of human O.T. give positive skin reactions as early as 3 days after an experimental infection with tuberculosis. These reactions are elicited for both human and bovine strains of tubercle bacilli, and appear to vary in intensity with the stage of infection, since the most pronounced reactions were obtained 7 and more days after the infection. In general, the maximum reaction appeared after 2 to 3 days and persisted for from 4 to 10 days. Although these local manifestations were consistently positive for the tuberculin derivatives, no reactions were observed after injection of O.T. There is some evidence, therefore, that these derivatives have a wider range of specificity for tuberculous infections and are sensitive to a high degree for the early diagnosis of bovine and human tuberculosis in guinea pigs.

As a corollary to these deductions, the next experiment shows that the derivatives have diagnostic value in obscure or latent tuberculosis in a mild form.

Series C: Two old guinea pigs, weighing about 650 gm. each, were injected subcutaneously with 0.05 mgm. of a human strain of tubercle bacilli which had been grown for 6 weeks on glycerine bouillon. A minute dose of an old culture was given with a view to produce, if possible, a limited tuberculous infection of the regional lymph nodes. The guinea pigs weighed approximately 860 gm. 129 days after the inoculation and, apart from slightly palpable inguinal lymph nodes, they were apparently healthy. This type of infection would correspond, in a measure, to a latent or clinically inactive tuberculosis. Intracutaneous injections of 0.02 cc. each of the acetyl and benzoyl derivatives and of O.T. (human) gave the following reactions:

Twenty-four hours after skin test: Acetyl Derivative: 1 x 0.5 cm., indurated, infiltrated and reddened; central whitish zone about 0.5 x 0.25 cm.

Benzoyl Derivative: 2 x 1 cm.; marked duration, infiltration and reddening; central white zone 0.5 x 0.5 cm.

Old Tuberculin: Flattened circular area 1 x 1 cm., with infiltration and indurated borders surrounding a central white zone 0.5 cm. in diameter. There was no appreciable erythema.

Forty-eight hours after test: Acetyl and benzoyl sites more intensely inflamed and beginning to show central umbilication and deep ulceration with some crusting (fig. 1).

Five days after test: Acetyl and benzoyl sites reduced in extent with diminished infiltration and reddening. O.T. site shows residual scar with crusting and no further local reaction.

Two weeks after test: Acetyl and O.T. sites of injection are negative. Benzoyl site shows deep central pitting and crusted surface; border of lesion is indurated and resembles a button ulcer.

Three weeks after test: Residual scarring at sites of injection but otherwise negative.

Series D: In this group of animals experiments were performed with the preparation which has been designated as *ether-insoluble "X."* Guinea pigs were inoculated in separate series with bovine and human strains of tubercle bacilli and intracutaneous injections were made after 4, 8, 15, 29, and 152 days after the initial infection. Control animals (uninoculated) were tested simultaneously. The results are summarized in table 3.

TABLE 3

GUINEA PIG	STRAIN AND DOSE IN MGM.	DOSE OF DERIV-ATIVE IN CC.	DAYS AFTER INFEC-TION	HEIGHT OF REAC-TION	DURATION OF REAC-TION	SIZE OF LESION
				days	*days*	
1	Human 0.2	0.02	4	3	4	0.75 x 0.4 cm., + *
2	Human 0.2	0.02	8	2	7	0.5 x 0.5 cm., ++
3	Human 0.4	0.02	15	2	10	1 x 1 cm., ++++
			29	1	12	2 x 1 cm., ++++
4	Bovine 0.4	0.02	15	1	8	2 x 1 cm., ++++
			29	2	10	1.5 x 1 cm., ++++
5	Human 0.05	0.02	152	2	18	2 x 1 cm., ++++
6	Uninoculated control	0.02				Negative
7	Uninoculated control	0.05				Negative

* + = moderate reaction; ++, strong; +++, severe; ++++, very intense.

The results of the experiment are decisive, and indicate that this preparation is very potent and possesses definite diagnostic properties in bovine and human tuberculosis in animals. The control guinea pigs gave uniformly negative results (figs. 2 to 6). Here again is shown the relation between dosage of tubercle bacilli, duration of infection and severity of the skin reactions. The local response can be elicited repeatedly in the course of the infection. In this connection it is significant that a typical reaction following intracutaneous injections of

acetyl and benzoyl derivatives does not interfere with the development of an intense local reaction in response to intracutaneous injections of *ether-insoluble "X."* This was observed in three animals (nos. 3, 4, 5) and is precisely the reverse of what occurs in uninoculated guinea pigs which have been treated with these derivatives prior to an intracutaneous injection of the "*X*" preparation. This observation lends itself to several possible interpretations which will be discussed in connection with the experiments on sensitization.

Sensitizing Properties of Tuberculin Derivatives

The requisite for a typical skin reaction with tuberculin is an infection with tuberculosis. Up to the present time no substance has been isolated or prepared from tuberculin that will sensitize the animal body to subsequent injections of the same material, or to its native unaltered tuberculin. Indeed, it is well known that an injection of tuberculin practised in tuberculous cattle a short time prior to a diagnostic skin test will "extinguish" a positive reaction which would take place otherwise. Within recent years Zinsser (16) and subsequently Petroff (17) have studied skin hypersensitiveness in guinea pigs which had been treated with a fraction of powdered tubercle-bacillus extract. This substance which they call a "nucleoprotein" fraction, as well as certain "residue" antigens from tubercle bacilli, are said to be capable of eliciting skin reactions in infected animals. Petroff, carrying the work of Zinsser further, believes that "such skin reactions cannot definitely be claimed to be identical with tuberculin hypersensitiveness." Further, he points out that the reactions fade more rapidly and never lead to deep injury of the tissues. As an added caution he would "hesitate to exclude the possibility that the reactions obtained with 'nucleoprotein' injections may have been due to minute amounts of unextracted fragments of tubercle bacilli." Skin hypersensitiveness, therefore, may be produced definitely by the injection of living or killed tubercle bacilli (Baldwin, Bessau, Petroff and others); and it may be evoked in questionable fashion by the injection of repeated doses of tubercle bacillus extracts or residues (Zinsser and Petroff). The experiments which are described below offer new evidence that sensitization can be produced by injection of the tuberculin derivatives which we have used.

Series A: Healthy guinea pigs were injected every 7 days with increasing doses of the derivatives, in separate series. At given inter-

TABLE 4

GUINEA PIG	DERIVATIVE	CC. INJECTED	INTRACUTANEOUS TEST	RESULT
1	Acetyl	0.5 1.0	Acetyl 0.1 cc., 11 days after first injection	Reaction in 24 hrs. with increased severity after 48 hrs. Lesion 1 x 1 cm., markedly reddened, infiltrated, with central whitish zone 2 mm. in diameter. Positive reaction for 16 days showing umbilication, necrosis and subsequent crusting and deep scarring
2	Acetyl	0.5 1.0	O.T., 0.05 cc., 11 days after first injection	Diffusely reddened, infiltrated elevated area, 2 x 1 cm., with central whitish zone 0.5 cm. Reaction very intense for next 6 days with border of lesion reddened and indurated and with deep central necrosis. Positive for 21 days and resulting in deep sloughing and scarring
3	Acetyl	0.5 1.0 1.0 2.0 2.5 3.0 2.5	O.T., 0.01 cc., acetyl, 0.02 cc., benzoyl, 0.02 cc., 49 days after first injection	24 hours after test the site of O.T. injection showed area 0.3 x 0.3 cm., reddened and infiltrated. Acetyl site, 0.5 x 0.5 cm., with more intense inflammation and infiltration and a central whitish zone 0.25 x 0.25 cm. Benzoyl site, area of inflammation and infiltration 1 x 0.75 cm. Positive reactions persisted for 5 days and left slight residual scarring. Benzoyl derivative gave most pronounced reaction and terminated with slight central pitting of site
4	Benzoyl	0.5 1.0	O.T., 0.05 cc., 11 days after first injection	Intense reaction after 48 hrs.; diffuse reddening, infiltration and swelling over area of 1.5 x 1 cm., with central whitish zone of 0.4 cm. Positive reaction for 12 days and terminating in deep scar at site
5	Benzoyl	0.5 1.0	Benzoyl 0.1 cc., 11 days after first injection	Intense reaction after 24 hours; diffuse reddening, infiltration and swelling over area of 0.5 x 0.5 cm., with central whitish zone of 0.2 cm. Periphery of lesion markedly reddened and indurated. Positive reaction for 7 days and terminating on tenth day with scarring at site

TABLE 4—*Continued*

GUINEA PIG	DERIVATIVE	CC. INJECTED	INTRACUTANEOUS TEST	RESULT
6	Acetyl	0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0	Ether-insoluble "X," 0.02 cc., 55 and 66 days after first injection	Negligible induration and reddening after 24 hours. Reaction questionable. After 48 hours site of injection free from local reaction
7	Benzoyl	0.5 1.0 1.5 2.0 2.5 3.0 3.0 4.0	Ether-insoluble "X," 0.02 cc., 66 days after first injection	Neglible induration and reddening after 48 hours
8	Benzoyl	0.5 1.0 1.5 2.0 2.5 3.0 3.0 4.0	Ether-insoluble "X," 0.02 cc., 66 days after first injection	Neglible induration and reddening after 48 hours
9	Control		Acetyl, 0.1 cc.	Transitory reddening after 24 hours with no residual changes
10	Control		Benzoyl, 0.1 cc.	Negative as in the preceding
11	Control		O.T., 0.05 cc.	Negative as in the preceding
12	Control		Ether-insoluble "X," 0.02 cc.	Negative as in the preceding

vals in the course of treatment, intracutaneous tests were made with each of the derivatives, O.T. and *ether-insoluble "X."* The results are summarized in table 4.

These experiments justify the conclusion that a sensitizing substance has been prepared from human O.T. of a kind that one or more

injections are capable of developing skin reactions in response to intracutaneous tests with the homologous or heterologous preparation or with unaltered O.T. That this sensitizing element is an integral part of the acetyl and benzoyl derivatives follows from the profound reactions which occur in guinea pigs which have been treated systematically with these preparations. The local response can be elicited at various times in the course of the treatment, but seems to be most marked in the early stages. The reactions are characterized by definite tissue changes, are persistent, and leave residual effects such as deep scarring and pigmentation. The negative results which were obtained with *ether-insoluble "X"* suggest that this preparation may differ in its properties, or that it may fail to elicit local reactions when the animal has progressed from a stage of sensitization to that of a definite resistance or immunity. In the experiments which have been described it was shown that this substance invariably produces a marked skin reaction in tuberculous guinea pigs in early and late stages of infection, and hence must contain within its nucleus an element common to it and the tubercle bacillus, in agreement with the properties of the other derivatives.

In this series of animals there were certain observations which appear to have some bearing on the question of sensitization. Whenever subcutaneous injections of the derivatives were preeated at the usual weekly intervals, old sites of previous injections, which had become scarred and faded, became intensely reddened and infiltrated and presented a picture of local flaring up. A secondary reaction of this type subsided after a few days. This phenomenon had its counterpart in another series of experiments which were devised to ascertain the effect of tuberculous infection on such local reactions. Another example of sensitization was seen in two guinea pigs which had been injected for periods of 7 and 8 weeks, respectively, with acetyl derivatives. Within a few minutes after injections made with the same material one week later, the animals became weak and dyspneic and showed signs of mild anaphylactic shock. Recovery was complete by next morning. During the ensuing week they lost 35 and 38 gm. in weight, respectively. In untreated animals of approximately the same age and weight no ill effects were observed with a single injection of 5 to 6 cc. subcutaneously.

Series B: Guinea pigs were injected every six to seven days with increasing amounts of tuberculin derivatives. At intervals during the treatment, and at a given time after the last injection, homologous and

TABLE 5

GUINEA PIG	DERIVATIVE	CC. INJECTED	INTRACUTANEOUS TEST	RESULT
1	Acetyl	0.5 1.0 1.2	Ether-insoluble "X," benzoyl and O.T., 0.02 cc. each, 2 weeks after first injection	Positive reaction after 24 hours. "X" site was reddened and indurated and entire lesion was 1 x 1 cm. O.T. site was reddened and indurated and measured 0.5 x 0.5 cm.; benzoyl site was reddened and indurated and measured 1 x 1 cm. (Fig. 7)
		1.5	Intracutaneous test repeated with 0.05 cc. each of same substances 16 days later, following the final injection of derivative	Intense reaction 24 hours later, maximum after 48 hours. The lesions measured 1 x 0.5 cm., 2 x 1.5 and 1.5 x 1.5 cm. for the "X," O.T. and acetyl derivative, respectively (fig. 8)
2	Ether-insoluble "X"	0.5 1.0 1.5 2.0	0.05 cc. each of acetyl and benzoyl derivatives and of ether-insoluble "X"	Marked reaction after 24 hours with reddening and induration of the areas. The sizes of the lesions were as follows: acetyl, 1 x 1 cm.; benzoyl, 1 x 1 cm.; ether-insoluble "X," 1.0 x 0.8 cm. (fig. 9)
3	Benzoyl	0.5 1.0 1.5	0.02 cc. each of ether-insoluble "X," O.T., and acetyl derivative	Intense reaction after 24 hours. Ether-insoluble "X," 1.5 x 1 cm.; O.T., 2 x 1 cm.; acetyl 1.5 x 1 cm. Erythema and induration pronounced
		1.5	Intracutaneous test repeated 16 days later with 0.05 cc. each of same materials	Intense reaction after 24 hours, maximum after 48 hours. Site of injections reddened and indurated, and surrounded by a zone of erythema. Ether-insoluble "X," 1 x 0.5 cm.; O. T., 2 x 1.5 cm.; acetyl, 1.5 x 1.5 cm. (fig. 10)
4	Ether-insoluble "X"	0.5 1.0 1.5	0.05 cc. O.T.	Marked reaction after 24 hours, maximum after 48 hours. Site of injection reddened and deeply infiltrated over an area of 2 cm. The lesion measured 1 x 1 cm. (fig. 11)
5	Control		Acetyl, 0.05 cc.	No reaction other than a transitory reddening which disappeared within 24 hours
6	Control		Benzoyl, 0.05 cc.	Negative
7	Control		Ether-insoluble "X," 0.05 cc.	Negative
8	Control		O.T. 0.05 cc.	Negative

heterologous derivatives and untreated O.T. were injected intracutaneously. In this series the skin tests were applied simultaneously, in order to test at a given time the range of reaction respecting the different substances which were used for sensitization. Two guinea pigs received acetyl and benzoyl derivatives of tuberculin, respectively, and two others were treated with *ether-insoluble "X."* All of the animals underwent treatment for the same length of time and received four separate injections. The doses ranged from 0.5 cc. for the first injection to 2 cc. for the final injection. Intracutaneous tests were made with 0.05 cc. in all but one instance. The results of this experiment were clear-cut and are summarized in table 5.

This experiment, similar to the preceding, demonstrates the sensitizing properties of acetylated and benzoylated derivatives of O.T. Any one of these substances appears to sensitize guinea pigs to the homologous or heterologous derivative as well as to O.T. In addition, there is evidence that the preparation *ether-insoluble "X"* sensitizes normal guinea pigs in a similar manner. Three injections of this substance have been found sufficient to elicit a typical skin reaction in response to an intracutaneous injection of O.T., acetyl or benzoyl derivative or *ether-insoluble "X."* Unlike the previous series of animals (series A), reactions to the last-named substance were more marked in the animals which had been treated with acetyl and benzoyl derivatives of tuberculin. Several factors might be mentioned here in this connection. The number of injections in the present series was three to four as compared with eight, and the total volume of material injected was one-sixth. Moreover, the intracutaneous test-dose of material was two and one-half times greater, namely, 0.05 cc. In accord with the previous statement regarding a possible difference in the sensitizing properties of *ether-insoluble "X"* and its chemical nature as compared with whole tuberculin and its derivatives, we have this additional evidence.

Series C: In this experiment a study was made of the effect of sensitization and its bearing upon symptoms of shock which had been observed in former experiments. Three normal guinea pigs were given several subcutaneous injections of the different preparations over a period of a few weeks. Twelve to fourteen days after the last injection a quantity of the homologous substance was injected intraperitoneally. The experiment was repeated twelve days later with the same results. In all of these animals shock symptoms came on at once following the intraperitoneal injection of 1.5 to 2 cc. of the derivatives. The animals

became restless immediately, then dyspneic and fell to one side. From this condition which lasted two to five minutes the animals lapsed into

TABLE 6

GUINEA PIG	WEIGHT	DERIVATIVE	SUBCUTANEOUS INJECTIONS	INTRAPERITONEAL INJECTION	RESULT
			cc.	*cc.*	
1	500	Acetyl	0.5		
	500	O.T.	1.0		
	520		1.2		
	515			1.5	Mild shock with dyspnea and restlessness. Recovery in 10 minutes
	575			1.5	Profound shock lasting 5 minutes. Recovery in 30 minutes
2	580	Benzoyl	0.5		
	560	O.T.	1.0		
	608		1.5		
	600			1.5	Mild shock lasting 2 minutes. Recovery in 20 minutes
	610			2.0	Severe shock for 5 minutes. Recovery in one hour
3	520	Ether-in-	0.5		
	510	soluble "X"	1.0		
	515			1.5	No shock
	560			2.0	Moderate shock with dyspnea and restlessness for 2 minutes. Recovery in 30 minutes
4	335	Control	Acetyl, 2.0 cc.	Intraperitoneal	No effect
5	320	Control	Benzoyl, 2.0 cc.	Intraperitoneal	No effect
6	345	Control	Ether-insoluble "X," 2.0 cc. intraperitoneal		No effect

a stupor of varying duration, from one-half to two hours. Recovery was complete. The results are summarized in table 6.

Series D: Guinea pigs were injected with human and bovine strains of tubercle bacilli. At intervals of one week subcutaneous injections of 1 cc. of acetyl derivative were given. The first dose was injected 11 to 21 days after the initial infection and the last one 36 to 44 days after infection. The results are summarized in table 7.

TABLE 7

GUINEA PIG	STRAIN	FIRST INJECTION OF DERIVATIVE	LAST INJECTION OF DERIVATIVE	RESULT
1	Human	11 days after infection	36 days after infection	Diffuse reddening over entire abdomen for 48 to 72 hours after each injection. Immediately after last dose animal fell to side with dyspnea, marked weakness, involuntary micturition and defecation. In distress for 20 minutes; on its feet and recovered gradually after 35 minutes. On following day site of injection was infiltrated and edematous with a central grayish zone. This reaction faded after 3 days
2	Human	11 days after infection	36 days after infection	Pale erythema after first injection. After succeeding injections flare-up over entire abdomen in 24 hours. Within 5 minutes after last injection an area of infiltration and edema, 3.0 x 3.0 cm., with a central purplish zone 1 x 1 cm. On following day edema was less and central zone became whitish. Reaction persisted 3 days
3	Human	11 days after infection	36 days after infection	Faint erythema after first injection and diffuse reddening over abdomen 24 hours after next dose. Within 2 minutes after last injection, an area of infiltration, 3.5 x 3 cm., with a central purplish zone 1.5 x 1 cm. On next day edema was reduced and central zone was grayish-white. Reaction persisted 4 days
4	Human	21 days after infection	36 days after infection	Diffuse reddening over entire abdomen changing to mottled areas of erythema after 48 hours. Old intracutaneous sites of injection flared up with intense erythema. Third injection was followed by erythema after 24 hours. Fourth and last dose produced an immediate local reaction area, 2 x 1 cm., with infiltration and edema and central purplish zone 1 x 0.5 cm. Reaction persisted 4 days with intense reddening and induration

TABLE 7—*Continued*

GUINEA PIG	STRAIN	FIRST INJECTION OF DERIVATIVE	LAST INJECTION OF DERIVATIVE	RESULT
5	Human	21 days after infection	44 days after infection	Twenty-four hours after first injection entire abdomen was reddened and sites of old intracutaneous injections were erythematous and indurated. A subcutaneous cold abscess flared up and became intensely reddened. A second dose was followed by a similar picture. After third injection, in 24 hours, intense diffuse reddening and flare-up of old subcutaneous sites of injection. On next day, ulceration and necrosis were marked. Lesion 3 x 1.5 cm. After last injection, slight erythema and fading in 24 hours (fig. 12)
6	Bovine	21 days after infection	36 days after infection	No local reactions at any time
7	Bovine	11 days after infection	36 days after infection	No local reactions followed first 3 injections. Twenty-four hours after last dose slight local infiltration and edema with grayish-white zone persisting until next day
8	Bovine	11 days after infection	36 days after infection	No local reactions after first 3 injections. Twenty-four hours after fourth and last dose, local infiltration and edema, 1 x 1 cm., with central purplish zone. On following day, central zone was grayish-white and reaction less intense
9	Bovine	15 days after infection	36 days after infection	Twenty-four hours after first injection, marked reddening and localized edema 4 x 2 cm. Next day erythema was patchy and old intracutaneous sites of injection were reddened and infiltrated (fig. 13). Twenty-four hours later abscess on abdomen was reddened. After second injection, marked diffuse reddening over entire abdomen. After third dose, slight erythema. After fourth and last injection, slight local edema and infiltration, grayish-white central zone
10*	Human	21 days after infection	44 days after infection	Questionable erythema 24 hours after first injection, limited to immediate site. Subsequent doses were not followed by flare-up or local reaction

* This guinea pig was a control experiment. The material used for repeated injection was prepared from tuberculin by precipitating it with methyl alcohol and dissolving the precipitate in the original volume of salt solution.

This series of experiments confirms in a more striking manner the previous observations which were made on uninoculated guinea pigs. In this group of animals an infection with tubercle bacilli serves to exaggerate the sensitizing properties of the derivatives to the extent that every injection is followed by an intense local reaction with a general flare-up at the sites of old faded areas. In addition to demonstrating a typical skin reaction which follows a subcutaneous dose of the tuberculin derivative, there is the added feature of a cumulative local sensitization, as well as of a more general hypersensitiveness. These conclusions would seem to be warranted on the basis of the shock symptoms which were elicited in some animals, and also because of the regular occurrence of intense local manifestations which appeared a few minutes after the injection of a derivative that had been used for systematic treatment. The formation of large wheals with intense edema, infiltration and erythema can be regarded as evidence of a local, if not of a general anaphylactic state. In keeping with the observations made with regard to altered antigenic specificity, the reactions were not so clear-cut in the animals which had been inoculated with bovine strains of tubercle bacilli. Although we have seen evidence of this wider range of activity for a heterologous infection, here we note that the same mechanism operates to develop a greater resistance to the derivative in question after an initial hypersensitiveness has been produced. Further study of this point is necessary, of course, yet the experimental findings suggest that our original hypothesis holds true, since it has been possible to develop in animals what appears to be a true immunity with this tuberculin derivative.

DISCUSSION

The results which have been reported in this paper establish two facts which appear to have considerable bearing upon the question of immunity to tuberculosis. It has been shown that certain derivatives prepared from tuberculin possess definite sensitizing properties and are of value in the diagnosis of bovine and human types of infection. With this as a starting point, it should be possible to isolate an active principle which will be free from nonspecific toxic substances and at the same time permit quantitative studies for standardization of the product. With this in mind, derivatives are being prepared from tuberculin obtained by growing tubercle bacilli on protein-free synthetic media.

The properties of the acetyl and benzoyl derivatives, which have been described, appear to be contingent upon a change in the protein molecule. The chemical basis for alteration of antigens to effect a change in the species specificity may be ascribed to the linkage of acetyl or benzoyl groups to the protein molecule. Thus Landsteiner and Jablons (18) explain the behavior of acetanhydride protein combinations which they studied. As to the precise mechanism, there is variance of opinion. In their work the loss of the Millon reaction suggested that the phenol hydroxyl in tyrosin was acetylated. The same phenomenon was observed by Schulze (19) in substituting the hydroxyl and amido groups in dibenzoyl tyrosin. Landsteiner and Jablons question whether the alteration of the tyrosin nucleus has any special significance regarding serological behavior. At all events, acetylation or benzoylation rendered tuberculin less specific in a serological sense by extending its range of activity to heterologous tubercle bacilli, and thus improving its diagnostic value for tubercle infections. This has been demonstrated in our experiments which have aimed to alter tuberculin so as to evoke or to augment sensitizing properties. The explanation for the results which were obtained may be found in a definite chemical change to which the tuberculin was subjected, since its solubility was radically altered in the first place. Rapid elimination of tuberculin in nontuberculous animals is doubtless a factor in its failure to sensitize or immunize. There is considerable evidence to show that tuberculous animals link tuberculous tissue with the tuberculin and thus elicit a typical reaction. Failure to assimilate tuberculin postulates the failure to sensitize. Experimentally, this was demonstrated some years ago by Franceschelli (20) who found that healthy guinea pigs and rabbits eliminated all traces of tuberculin after six hours. Apart from this consideration there are other factors which relate to concentrating an active principle and making it more available, and, what is most probable, unlocking a sensitizing radicle by impressing it with chemical properties which distinguish it from the original crude tuberculin.

From the standpoint of tuberculin hypersensitiveness and true anaphylaxis, our experiments have adduced certain facts which seem to controvert the well-known fixed belief that these two types of reaction are more or less distinct. Zinsser (21), confirming the early work of Baldwin and using the isolated uterus technique, showed that skin hypersensitiveness and true anaphylactic reactions did not run parallel. Similarly, Smith (22), and Dietrich and Klopstock (23), more recently

have presented evidence of like import. Smith's studies, in particular, are of interest from our own viewpoint in that he was able to demonstrate the complete lack of relationship between tuberculin and tuberculoprotein with regard to their sensitizing properties as studied by the isolated uterus method. Significant in this connection is his statement to the effect that there "is no apparent relation between the tuberculin reaction and the anaphylactic state which may or may not exist in the experimentally infected animal." It is to be noted that all of these studies were concerned with tubercle bacilli or their extracts and not with derivatives of tuberculin.

With regard to the types of skin reaction that may occur in tuberculous animals, it is important to differentiate nonspecific from the typical specific manifestations. The nature of the tuberculin reaction remains to be settled, albeit we have ample study to support the idea that the genuine picture of histological tuberculosis occurs only in the presence of hypersensitiveness to the infection and as such is conditioned by soluble tuberculous materials. With this conception in mind, Zieler (24) explains on a toxic basis all reactions that may occur with dialysates from bacterial residues and such as are free from bacterial elements. The specificity of the tuberculin reaction has been called into question by investigators who have failed to recognize the essential difference between a transitory local reaction and a deep-seated tissue change which is elicited under proper conditions by tuberculin. The former type of reaction, referable to a toxic element, occurs not only in tuberculous individuals, but also in response to heterologous formed and unformed proteins, and as such must be distinguished from the true reaction which is delayed in its appearance and persists longer. Clinical studies made recently by Casini (25) and Moewes (26) call attention to this fact. Along similar lines we find much that is controversial regarding the nature of the active substance of tuberculin. In analyzing the chemical reactions of the so called "nucleoprotein" substance prepared by Zinsser from the tubercle bacillus, we are impressed by the striking similarity of these to the known behavior of albumoses in general. Although Löwenstein and Pick (27) were able to obtain typical tuberculin reactions with tuberculin freed from albumoses and peptones, it appears from more recent work by Bouveyron (28) that the ability of tuberculin to induce cutaneous reactions is completely destroyed by those substances that precipitate the albumoses completely or in part. Irrespective of whether or not the

albumoses represent the active substance of tuberculin, it is pertinent to examine certain facts which have been brought out in the early investigations that were made by Krehl and Matthes (29) and Kirchheim and Tuczek (30). They were able to prove experimentally that albumoses, regardless of their origin, are capable of exerting toxic action in tuberculous guinea pigs and are related in their action to that of tuberculin. A manifest difference, however, was pointed out in connection with the lack of intensity and regularity of reactions from albumoses. The criticism which might be directed toward the products of tubercle bacilli with these points in mind could apply with equal force to our own tuberculin derivatives but for the fact that we have been able to demonstrate typical deep-seated and persistent skin reactions with the products which have been studied under controlled conditions of experimental infection.

Ether-insoluble "X" substance, which has been studied in a preliminary way, represents probably an amino acid or a lecithin-like substance arising from the metabolism of tubercle bacilli and will be described more fully in a subsequent report. This preparation sensitizes and gives reactions analogous to tuberculin and is of definite value in diagnosing a type of infection which remains undetected with the use of O.T. of human or bovine origin. Chemical studies of tubercle bacilli have given us interesting data bearing on the problem of essential reacting substances which appear to reside in the cell-body and to occur outside as products of metabolism or perhaps as specific sensitizing elements. From this standpoint the studies of Goris (31) and of Long (32) are of significance in regard to the part played by amino acids which can be detected in the bacilli. Our own studies with *ether-insoluble "X"*, which was prepared from tuberculin, suggest a field for further investigation, inasmuch as the active substance represents a minute fraction of the original tuberculin.

SUMMARY AND CONCLUSIONS

1. Three derivatives have been prepared from human O.T. and have been shown to be potent and capable of eliciting typical skin reactions in tuberculous guinea pigs. The derivatives were prepared (1) by acetylation, (2) by benzoylation and (3) fractionation and precipitation with alcohol and ether.

2. These derivatives are sensitive and have a wider range of diagnostic specificity than that of ordinary O.T. In the experimental animal

and in patients these preparations have been found of value in detecting infection with a heterologous strain of tubercle bacilli.

3. In tuberculous guinea pigs the derivatives elicit typical skin reactions upon intracutaneous injection as early as three days after infection with human or bovine strains of tubercle bacilli.

4. Skin reactions which develop after intracutaneous tests are characterized by deep-seated tissue changes, infiltration and edema, and terminate in typical necrosis, with scarring and residual pigmentation. The reactions persist for several days to two weeks and are of variable extent and severity depending upon the stage of infection.

5. The derivatives of tuberculin have definite sensitizing properties, which can be demonstrated in healthy animals as well as in those which have been infected with both human and bovine tuberculosis. One or more injections of any one of the preparations suffice for the development of skin reactions in response to intracutaneous tests made with the homologous or heterologous derivative or with O.T. Local and general anaphylactic reactions have been produced in infected guinea pigs and, to a lesser degree, in healthy animals which have been treated systematically with derivatives for varying lengths of time.

6. Evidence has been adduced to show that an initial state of hypersensitiveness may progress to that of a definite resistance or immunity.

7. The experiments at this stage suggest that there is a relation between immunological specificity and chemical structure of antigens which can be applied to tuberculins for the purpose of diagnosis and sensitization. As a corollary to these findings, evidence at hand points to the isolation of an active principle and a possible interpretation of the mechanism of the tuberculin reaction.

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FIG. 1. GUINEA PIG INOCULATED WITH HUMAN STRAIN OF TUBERCLE BACILLI 129 DAYS PRIOR TO INTRACUTANEOUS TEST

Reaction 48 hours after test with human O.T. (*T*), acetyl derivative (*A*), benzoyl derivative (*B*).

FIG. 2. GUINEA PIG INOCULATED WITH HUMAN STRAIN OF TUBERCLE BACILLI 15 DAYS PRIOR TO INTRACUTANEOUS TEST WITH ETHER-INSOLUBLE "X"

Reaction 48 hours after test (*B*), with flare-up of cold abscess at (*A*)

FIG. 3. SAME GUINEA PIG WITH TEST REPEATED 29 DAYS AFTER INFECTION

Reaction 48 hours after test

FIG. 4. GUINEA PIG INOCULATED WITH BOVINE STRAIN OF TUBERCLE BACILLI 15 DAYS PRIOR TO INTRACUTANEOUS TEST WITH ETHER-INSOLUBLE "X"

Reaction 48 hours after test

FIG. 5. SAME GUINEA PIG WITH TEST REPEATED 29 DAYS AFTER INFECTION

FIG. 6. REACTION TO INTRACUTANEOUS ETHER-INSOLUBLE "X" IN GUINEA PIG INOCULATED WITH HUMAN BACILLI 152 DAYS PREVIOUSLY

FIG. 7. INTRACUTANEOUS TESTS IN NORMAL GUINEA PIG TREATED WITH ACETYL DERIVATIVE

Reactions 48 hours after test with ether-insoluble "X" (*A*), benzoyl derivative (*B*), and O.T. (*C*). (*D*) is the site of a lesion which developed two days after second injection of sensitizing derivative. It measured 1.5 x 1 cm.

FIG. 8. SAME GUINEA PIG AS IN FIG. 7, 18 DAYS LATER, SHOWING SKIN REACTIONS WITH ETHER-INSOLUBLE "X" (*A*), BENZOYL DERIVATIVE (*B*), AND O.T. (*C*)

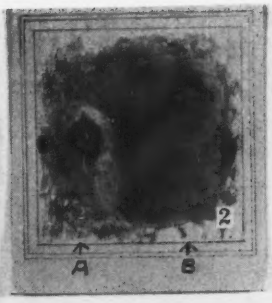
FIG. 9. INTRACUTANEOUS TESTS IN NORMAL GUINEA PIG TREATED WITH ETHER-INSOLUBLE "X"

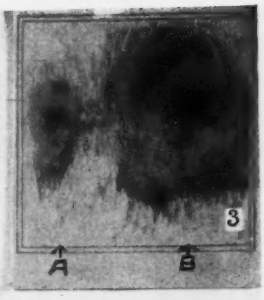
Reactions 48 hours after tests with acetyl derivative (*A*), benzoyl derivative (*B*), and ether-insoluble "X" (*X*).

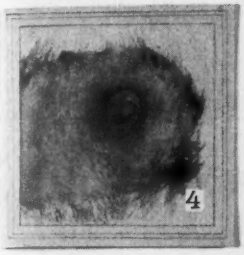
FIG. 10. NORMAL GUINEA PIG TREATED WITH BENZOYL DERIVATIVE

Intracutaneous tests with ether-insoluble "X" (*X*), O.T. (*C*), and acetyl derivative (*A*). Reactions 48 hours after test.

T
B
A
1

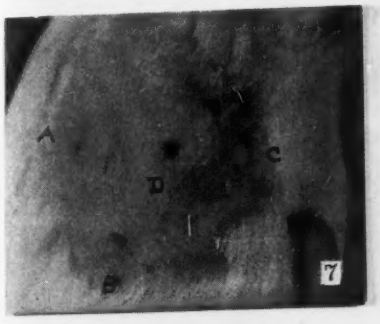

A
B
2

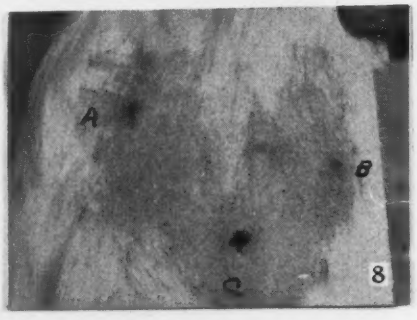

A
B
3

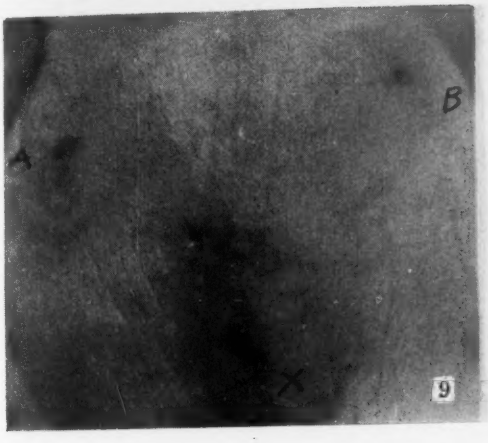

4

5

6


A
D
C
B
7


A
B
C
8


A
B
X
9

X
C
A
10

FIG. 11. NORMAL GUINEA PIG TREATED WITH ETHER-INSOLUBLE "X", SHOWING REACTION TO INTRACUTANEOUS INJECTION OF O.T. (*C*)

Lesion 48 hours old

FIG. 12. DEEP TISSUE CHANGES IN GUINEA PIG INOCULATED WITH HUMAN TUBERCLE BACILLI AND INJECTED SUBCUTANEOUSLY WITH ACETYL DERIVATIVE

This reaction occurred 48 hours after the third dose, which was given 35 days after initial infection.

FIG. 13. REACTION TO SUBCUTANEOUS INJECTION OF ACETYL DERIVATIVE IN GUINEA PIG INFECTED WITH BOVINE BACILLI 15 DAYS PREVIOUSLY

Areas (*A*), (*B*) and (*C*) represent flare-up at sites of old intracutaneous tests

FIG. 14. PIRQUET TECHNIQUE WITH ETHER-INSOLUBLE "X" IN CHILD WHO REACTED TO BOVINE O.T. ONLY

Reaction 48 hours old

FIG. 15. REACTION (PIRQUET) TO BENZOYL DERIVATIVE IN CHILD WHO REACTED TO BOVINE O.T. ONLY

Lesions (*A*) and (*B*) and control (*C*), 48 hours after test

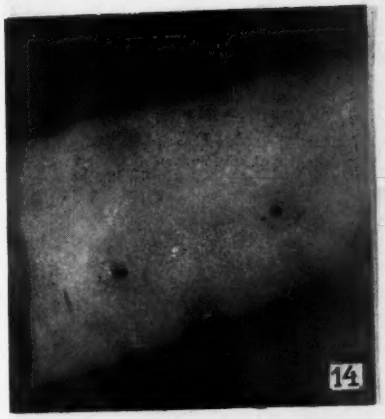
FIG. 16. SAME PATIENT AS IN FIG. 14, 48 HOURS AFTER TESTS WITH ACETYL DERIVATIVE (*B*) AND BENZOYL DERIVATIVE (*A*). CONTROL AT (*C*)

FIG. 17. SAME PATIENT AS IN FIG. 15, 48 HOURS AFTER TEST WITH ACETYL DERIVATIVE (*A*) AND (*B*). CONTROL AT (*C*)

C
11

12

A
B
C
13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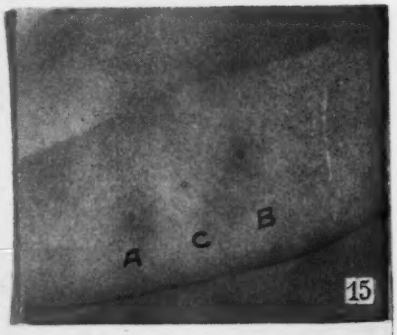
A
C
B
15

A
C
B
16

A
C
B
17

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